IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GALDERMA LABORATORIES, L.P., GALDERMA S.A. and GALDERMA RESEARCH AND DEVELOPMENT, S.N.C.	:	
Plaintiffs,	:	
v.	:	C.A. No. 10-45-LPS
TOLMAR, INC.,	:	
Defendant.	:	

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OPINION

UNSEALED ON
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September 11, 2012
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STARK, U.S. District Judge:

INTRODUCTION

Plaintiffs, Galderma Laboratories, L.P. ("Galderma Labs"), Galderma S.A., and Galderma Research and Development, S.N.C. ("Galderma R&D") (collectively, "Galderma"), market a topical anti-acne medication containing 0.3% by weight adapalene under the trade name Differin® Gel, 0.3%. The Food and Drug Administration ("FDA") Orange Book lists United States Patent Nos. 7,579,377 ("the '377 patent"); 7,737,181 ("the '181 patent"); 7,838,558 ("the '558 patent"); 7,834,060 ("the '060 patent"); and 7,868,044 ("the '044 patent") in connection with Galderma's Differin® Gel, 0.3% product.

On September 14, 2009, Defendant, Tolmar, Inc. ("Tolmar"), filed an Abbreviated New Drug Application ("ANDA") seeking approval to market a generic version of Galderma's Differin® Gel, 0.3%. In January 2010, Galderma initiated this litigation against Tolmar in connection with the Paragraph IV certifications contained in Tolmar's ANDA.

The Court held a bench trial from March 5 through March 14, 2012. Tolmar disputed infringement with respect to certain claims of the patents-in-suit,[1] contends the patents-in-suit are invalid under 35 U.S.C. §§ 102, 103, and 112, and also asserts inequitable conduct and lack of standing. The parties completed post-trial briefing on April 30, 2012. (D.I. 316; D.I. 317; D.I. 330; D.I. 331)[2]

Tolmar received tentative FDA approval to market its generic 0.3% adapalene product on March 14, 2012. On June 4, 2012, the Court enjoined Tolmar from launching its generic version

[1] Galderma did not assert the '377 patent at trial.

[2] In addition to a total of 200 pages of post-trial briefs, the parties together filed an additional 558 pages of proposed findings of fact and conclusions of law. The combined number of proposed findings of fact was more than 1500. The astounding length of the parties' post-trial submissions contributed substantially to the length of time it has taken to complete this Opinion, as well as to the size of this Opinion.

of 0.3% adapalene until the Court issued its opinion resolving the disputed issues in this case. (D.I. 334) The 30-month stay expired on June 10, 2012.

As explained below, the Court finds in favor of Plaintiffs on all issues with the limited exception of standing with respect to one of the Plaintiffs.

FINDINGS OF FACT

I. BACKGROUND

A. Nature and Stage of the Proceedings

1. Galderma markets a topical anti-acne medication containing 0.3% by weight of adapalene under the trade name Differin® Gel, 0.3%. (PTX 301)

2. Tolmar has filed an ANDA seeking approval to market a generic version of Galderma's Differin® Gel, 0.3%. Tolmar's ANDA application with Paragraph IV certifications constituted an act of infringement under 35 U.S.C. § 271(e)(2). (*See* D.I. 1; D.I. 44)

3. Tolmar received tentative approval from the FDA on March 14, 2012 to market its generic 0.3% adapalene product. (*See* Tr. at 1976:20-22.) The thirty-month stay barring Tolmar from marketing its drug expired June 10, 2012. (*See* D.I. 287, Exh. 1, Uncontested Fact 48; 21 U.S.C. § 355(j)(5)(B)(iii); 21 C.F.R. § 314.107(b)(3))

B. Key Players

4. Dr. Michael Graeber is a named inventor on the Galderma patents-in-suit. (PTX 1-5) Dr. Graeber is currently employed by Galderma R&D. Dr. Graeber has a medical degree and clinical experience in treating patients with various dermatological conditions, including acne. (Tr. at 295:25-297:13)

5. Dr. Janusz Czernielewski is a named inventor on the Galderma patents-in-suit. (PTX 1-5) Dr. Czernielewski is currently employed by Galderma. Dr. Czernielewski has a medical degree with a specialty in dermatology, a Ph.D. in Immunology, and an MBA. He has

clinical experience in treating patients with various dermatological conditions, including acne. (Tr. at 1768:22-1772:13)

6. Dr. Braham Shroot is a former employee of Galderma, the named inventor on the "Shroot patents," and an author of several articles discussed during trial. (Tr. at 956:20-957:7)

7. Dr. Michael T. Goldfarb is a dermatologist at the University of Michigan and named author on the "Goldfarb photodamage" references discussed during trial. (Tr. at 1291:19-22)

8. Dr. Seth J. Orlow is an expert witness proffered by Galderma. Dr. Orlow is an attending physician in dermatology and pediatrics with a focus on treating children and adolescents; he is also Director of the Dermatology Service at the NYU Langone Medical Center. Dr. Orlow has an M.D. and a Ph.D. in Molecular Pharmacology from Albert Einstein College of Medicine. (PTX 106) Dr. Orlow has experience running dose response curves, specifically for retinoids. (Tr. at 1237:23-1238:14)

9. Dr. Diane Thiboutot is an expert witness proffered by Galderma. Dr. Thiboutot is a dermatologist and professor of dermatology at the Pennsylvania State University, Milton S. Hershey Medical Center. Dr. Thiboutot has first-hand experience with the clinical trials that led to the approval of Galderma's 0.3% adapalene product. (*See* Tr. at 1378:11-1386:25)

10. Dr. Kenneth A. Walters is an expert witness proffered by Galderma. Dr. Walters is the Director of Research and Development and Business Development at An-eX Analytical Services Ltd., a contract service provider, where he has managed over 200 projects developing and contributing to the development of dermatological and transdermal systems containing a variety of drugs. (Tr. at 83:21-87:24)

11. Dr. Ronald Thisted is an expert witness proffered by Galderma. Dr. Thisted is currently Chair of the Department of Health Studies at the University of Chicago, a department within the Pritzker School of Medicine and the Division of Biological Sciences at the University. Dr. Thisted received his Ph.D. in statistics from Stanford in 1977. (PTX 115) Dr. Thisted offered testimony concerning the statistical issues in the case.

12. Mr. John Jarosz is an expert witness proffered by Galderma. Mr. Jarosz is the managing principal of Analysis Group, Inc., an economic, financial, and strategy consulting firm, and Director of the firm's Washington, D.C. office. (PTX 120)

13. Dr. Howard Maibach is an expert witness proffered by Tolmar. Dr. Maibach received his Doctorate of Medicine from Tulane University and has practiced in the field of dermatology since 1961. (Tr. at 930:12-931:9, 931:15-23)

14. Dr. Russell O. Potts is an expert witness proffered by Tolmar. Dr. Potts has worked extensively on research relating to skin barrier function and the development of topical drug delivery products for nearly the past 30 years. (Tr. at 223:6-21, 224:11-225:7, 227:18-229:2)

15. Dr. Marcello Pagano is an expert witness proffered by Tolmar. Dr. Pagano is a Professor of Statistical Computing at the Harvard School of Public Health, as well as a Senior Scientist at The Children's Hospital in Boston. (Tr. at 620:6-25)

16. Dr. Thomas D. Vander Veen is an expert witness proffered by Tolmar. Dr. Vander Veen is a Director at Navigant Economics, a global economic consulting firm. (Tr. at 1648:8-13)

C. The Claimed Invention—Adapalene Gel, 0.3%

17. 0.3% adapalene gel, marketed by Galderma as Differin® Gel, 0.3%, was approved in 2007, and is one of the most recent retinoid analog products on the market for the treatment of acne. (PTX 301 at GAL000056165)

18. Differin® Gel, 0.1% (containing 0.1% by weight adapalene) was approved by the FDA in 1996 for the treatment of acne. (PTX 255)

19. The use of Galderma's Differin® Gel, 0.3% has been shown to reduce lesion counts and improve acne when compared to 0.1% adapalene, while at the same time maintaining comparable tolerability. (PTX 1-5 at Figures 1-3 and Examples 2-3; PTX 231 at 244-49; PTX 212 at 358 ("demonstrating equivalent tolerability"))

20. The Galderma patents-in-suit claim priority from a French application, FR 02 03070, filed on March 12, 2002, and the patents contain similar specifications. (PTX 42) All of the asserted claims of the patents-in-suit are entitled to the March 12, 2002, priority date.[3]

21. The patents' specifications indicate that "it has now surprisingly been shown that, in addition to exhibiting better therapeutic efficacy compared to known compositions, the compositions according to the invention exhibits good tolerance, comparable to those of the known compositions with a lower concentration of active principle." (*E.g.*, PTX 3 at 2:24-29)

22. The specifications note that the "pharmaceutical composition containing 0.3% of adapalene exhibits a benefit/risk ratio which makes it particularly suitable for the treatment of dermatological maladies having an inflammatory or proliferative component, and in particular, common acne." (*E.g.*, PTX 3 at 6:52-57)

23. The patents-in-suit contain data from the Phase II clinical trials with adapalene. The results of these trials show that 0.3% adapalene was more effective than 0.1% adapalene

[3] Tolmar's contention that certain claims of the '181 and '044 patents are not entitled to the March 12, 2002 priority date are addressed later in this Opinion.

while at the same time maintaining a comparable tolerability profile to 0.1% adapalene. (*E.g.*, PTX 3 at Figures 1-3, Examples 2-3)

24. For example, the patents state:

> These observations lead to the following conclusions: the 0.3% adapalene gel acts more rapidly than the 0.1% adapalene gel; specifically, from the fourth week of treatment, a difference is noted between the effectiveness of the 0.1% adapalene gel and the 0.3% adapalene gel; the 0.3% adapalene gel produces a clearly greater therapeutic effect after 8 weeks of treatment.

(*E.g.*, PTX 3 at 5:30-36)

25. The patents also include the following table:

Local undesirable effects	0.3% adapalene gel (N = 70)	0.1% adapalene gel (N = 70)	Vehicle gel (N = 74)
Skin and secondary structures (nails, hair)	31 (44.3%)	28 (40.0%)	5 (6.8%)
Dry skin	16 (22.9%)	13 (18.6%)	2 (2.7%)
Erythema	8 (11.4%)	3 (4.3%)	0 (0.0%)
Skin discomfort	8 (11.4%)	7 (10.0%)	0 (0.0%)
Desquamation	6 (8.6%)	5 (7.1%)	0 (0.0%)
Dermatitis	3 (4.3%)	1 (1.4%)	0 (0.0%)
Pruritos	3 (4.3%)	1 (1.4%)	1 (1.4%)
Irritant dermatitis	2 (2.9%)	7 (10.0%)	0 (0.0%)
Local allergic reactions	1 (1.4%)	0 (0.0%)	0 (0.0%)
Pediculosis	1 (1.4%)	0 (0.0%)	0 (0.0%)
Contact dermatitis	1 (1.4%)	0 (0.0%)	0 (0.0%)
Insolation	1 (1.4%)	3 (4.3%)	1 (1.4%)
Burning sensation	1 (1.4%)	0 (0.0%)	0 (0.0%)
Urticaria	1 (1.4%)	0 (0.0%)	0 (0.0%)
Infection	1 (1.4%)	0 (0.0%)	0 (0.0%)
Excoriation	0 (0.0%)	0 (0.0%)	1 (1.4%)
Eczema	0 (0.0%)	0 (0.0%)	1 (1.4%)
Oedema	0 (0.0%)	1. (1.4%)	0 (0.0%)

(*E.g.*, PTX 3 at 6:23-41)

26. The patents state, "[f]rom this table, it is noted that the occurrence of undesirable side effects is statistically the same for the two gels with the different concentrations of active agent." (PTX 3 at 6:43-45)

27. This sentence is correct as the differences between the adverse events reported in the table with the 0.3% adapalene gel and the 0.1% adapalene gel are not statistically significant. (Tr. at 1494:2-14; 1496:14-23)

28. The patents then state that "[t]he intensity of the undesirable side effects is average, which leads to the conclusion that the two gels are well-tolerated by the patients." (*E.g.*, PTX 3 at 6:45-47)

29. Galderma also conducted Phase III clinical trials in order to obtain market approval from the FDA to sell a 0.3% adapalene product. In conducting the trials, the FDA required Galderma to compare the efficacy of the 0.3% adapalene product to the 0.1% adapalene product, as well as to a control vehicle, in order to gain FDA approval. (PTX 307 at GAL000033735; Tr. at 1410:16-20; *see also* Tr. at 1411:25-1412:5 (Dr. Thiboutot testifying that "[t]he protocol and the statistical analysis package were agreed upon with the FDA prior to the initiation of [the U.S. Phase III] trial"))

30. The results of these trials confirmed that 0.3% adapalene gel was more effective than both the vehicle control and the 0.1% adapalene product; the FDA approved the 0.3% adapalene product in June 2007. (PTX 301; PTX 307 at GAL000033743; Tr. at 1411:2-24; 1412:6-10)

31. The U.S. Phase III trial also highlighted the unexpected tolerability profile of adapalene 0.3% gel. (PTX 231 at 248; Tr. at 1260:3-15; 1425:18-1426:1; 1427:21-1428:1) This clinical trial also demonstrated that with both adapalene 0.3% and adapalene 0.1% gel, the severity of most of the patient-reported adverse events and physician-reported local tolerability assessments was low and their effects were transient. (PTX 231 at 245-46, 248; Tr. at 1426:12-1427:12; 1412:20-24; 1416:9-1417:16; 1418:13-1419:18; 1421:5-1425:11)

32. Additionally, of the 258 patients in the adapalene 0.3% group, only three withdrew due to an adverse event, compared to two patients out of 261 in the adapalene 0.1% group, and one out of 134 in the gel vehicle group. (PTX 231 at 246; Tr. at 1425:13-17)

33. The publication reporting the results from the Phase III study specifically states that "[b]oth concentrations of adapalene gel were safe and well tolerated in this study. The signs and symptoms of skin irritation were mostly mild to moderate in severity and transient in nature. Importantly, despite the increase in adapalene concentration, the incidence of severe skin irritation was low and comparable between the two treatment groups." (PTX 231 at 248)

34. In a book chapter published in 2010, Tolmar's expert, Dr. Maibach, concluded that this paper demonstrated statistical superiority of 0.3% adapalene over 0.1% adapalene "while demonstrating ***equivalent tolerability.***" (PTX 212 at 358 (emphasis added); Tr. at 1128:4-17)

35. All of the claims asserted at trial recite the 0.3% adapalene gel for use in the treatment of acne, and some more specifically recite common acne. (PTX 2 at claims 2, 35, and 36; PTX 3 at claims 5, 24, and 27; PTX 4 at claims 4 and 5; PTX 5 at claims 3, 40, and 41)

36. Galderma's Differin® Gel, 0.3% is a 0.3% by weight adapalene gel and is approved by the FDA for use in the treatment of acne. (PTX 301)

37. Galderma's Differin® Gel, 0.3% is the commercial embodiment of the claims asserted in this litigation. (PTX 301; Tr. at 1265:13-16) Tolmar does not dispute that Galderma's Differin® Gel, 0.3% is an embodiment of the claims asserted in this litigation.

38. The Galderma patents-in-suit asserted against Tolmar at trial (the '181 patent, the '044 patent, the '558 patent, and the '060 patent) are directed towards 0.3% adapalene compositions that are effective for the treatment of acne or common acne and/or methods of

using 0.3% adapalene compositions for the treatment of acne or common acne. (PTX 2-5) The '060 patent and the '044 patent contain claims reciting methods of effectively treating common acne or acne, using pharmaceutical compositions containing 0.3% adapalene. The '181 patent and the '558 patent contain claims to effective pharmaceutical compositions containing 0.3% adapalene for the treatment of acne or common acne.

D. Priority Dates, Expiration, and Asserted Claims of the Patents-in-Suit

39. U.S. Patent Application No. 10/937,612, from which the '377 patent issued, was filed in the United States Patent and Trademark Office ("PTO") on September 10, 2004. (PTX 1; PTX 6)

40. The '377 patent, entitled "Administration of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid for the Treatment of Dermatological Disorders," issued on August 25, 2009, naming Michael Graeber and Janusz Czernielewski as the inventors, and listing Galderma Research & Development, Biot (FR) as the assignee. (PTX 1; PTX 6.)

41. The '377 patent claims priority from Provisional Application No. 60/370,223, filed on April 8, 2002, and French Application No. 02 03070, filed on March 12, 2002. (PTX 1; PTX 6)

42. The '377 patent is a continuation of PCT Application No. PCT/EP03/03246, filed on March 12, 2003. (PTX 1; PTX 6)

43. The PTO issued a Certificate of Correction on November 4, 2010 for the '377 patent term adjustment. (PTX 1 at GAL000277171)

44. The '377 patent is currently owned by Galderma Research & Development, S.N.C. and expires on September 10, 2026. (PTX 19; PTX 55-59; D.I. 287, Exh. 1, Uncontested Fact 15)

45. U.S. Patent Application No. 11/494,693, from which the '181 patent issued, was filed in the PTO on July 28, 2006. (PTX 2; PTX 20)

46. The '181 patent, entitled "Pharmaceutical Compositions Comprising 0.3% By Weight of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid for the Treatment of Dermatological Disorders," issued on June 15, 2010, naming Michael Graeber and Janusz Czernielewski as the inventors, and listing Galderma Research & Development, Biot (FR) as the assignee. (PTX 2; PTX 20)

47. The '181 patent claims priority from Provisional Application No. 60/370,223, filed on April 8, 2002, and French Application No. 02 03070, filed on March 12, 2002. (PTX 2; PTX 20)

48. The '181 patent is a continuation-in-part of U.S. Patent Application No. 10/937,612, filed on September 10, 2004 and issued as the '377 patent, which is a continuation of PCT Application No. PCT/EP03/03246, filed on March 12, 2003. (PTX 2; PTX 20)

49. The '181 patent is terminally disclaimed to the '377 patent, U.S. Patent No. 7,642,288, and U.S. Patent Application Nos. 12/437,008 (which issued as the '060 patent) and 12/103,182 (which issued as the '558 patent). (PTX 2; PTX 20)

50. The '181 patent is currently owned by Galderma Research & Development, S.N.C. and expires on March 12, 2023. (PTX 19; PTX 32; PTX 55-59; D.I. 287, Exh. 1, Uncontested Fact 23)

51. Galderma asserted at trial that Tolmar infringes claims 35 and 36 of the '181 patent, and Tolmar has conceded infringement of those claims. (Tr. at 53:14-17)

52. U.S. Patent Application No. 12/437,008, from which the '060 patent issued, was filed in the PTO on May 7, 2009. (PTX 3; PTX 33)

53. The '060 patent, entitled "Administration of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid for the Treatment of Dermatological Disorders," issued on November 16, 2010, naming Michael Graeber and Janusz Czernielewski as the inventors, and listing Galderma Research & Development, Biot (FR) as the assignee. (PTX 3; PTX 33)

54. The '060 patent claims priority from Provisional Application No. 60/370,223, filed on April 8, 2002, and French Application No. 02 03070, filed on March 12, 2002. (PTX 3; PTX 33)

55. The '060 patent is a continuation of U.S. Patent Application No. 10/937,612, filed on September 10, 2004 and issued as the '377 patent, which is a continuation of PCT Application No. PCT/EP03/03246, filed on March 12, 2003. (PTX 3; PTX 33)

56. The '060 patent is terminally disclaimed to the '377 patent, U.S. Patent No. 7,642,288, and U.S. Patent Application No. 12/103,182 (which issued as the '558 patent). (PTX 3; PTX 33)

57. The '060 patent is currently owned by Galderma Research & Development, S.N.C. and expires on March 12, 2023. (PTX 19; PTX 32; PTX 55-59; D.I. 287, Exh. 1, Uncontested Fact 31)

58. Galderma asserted at trial that Tolmar infringes claims 24 and 27 of the '060 patent. Tolmar has conceded infringement of claim 24, but denies that it infringes claim 27. (Tr. at 53:14-17) However, Tolmar has stipulated that if claim 27 of the '060 patent is held valid and enforceable, and if Tolmar's formulation is found equivalent to the claimed formulation, and finally if prosecution history estoppel does not apply, Tolmar will induce infringement of that claim. (Tr. at 72:13-73:2)

59. U.S. Patent Application No. 12/103,182, from which the '558 patent issued, was filed in the PTO on April 15, 2008. (PTX 4; PTX 37)

60. The '558 patent, entitled "Administration of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid for the Treatment of Dermatological Disorders," issued on November 23, 2010, naming Michael Graeber and Janusz Czernielewski as the inventors, and listing Galderma Research & Development S.N.C., Valbonne (FR) as the assignee. (PTX 4; PTX 37)

61. The '558 patent claims priority from Provisional Application No. 60/370,223, filed on April 8, 2002, and French Application No. 02 03070, filed on March 12, 2002. (PTX 4; PTX 37)

62. The '558 patent is a divisional of U.S. Patent Application No. 10/937,612, filed on September 10, 2004, and issued as the '377 patent, which is a continuation of PCT Application No. PCT/EP03/03246, filed on March 12, 2003. (PTX 4; PTX 37)

63. The '558 patent is terminally disclaimed to the '181 patent and U.S. Patent Application No. 11/494,69 (which issued as the '181 patent). (PTX 4; PTX 37)

64. The '558 patent is currently owned by Galderma Research & Development, S.N.C. and expires on March 12, 2023. (PTX 19; D.I. 287, Exh. 1, Uncontested Fact 35)

65. Galderma asserted at trial that Tolmar infringes claim 5 of the '558 patent, and Tolmar has conceded that it infringes this claim. (Tr. at 53:14-17)

66. U.S. Patent Application No. 12/772,861, from which the '044 patent issued, was filed in the PTO on May 3, 2010. (PTX 5; PTX 47)

67. The '044 patent, entitled "Method for the Treatment of Acne Using Compositions Comprising 0.3% By Weight of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid," issued

on January 11, 2011, naming Michael Graeber and Janusz Czernielewski as the inventors, and listing Galderma Research & Development, Biot (FR) as the assignee. (PTX 5; PTX 47)

68. The '044 patent claims priority from Provisional Application No. 60/370,223, filed on April 8, 2002, and French Application No. 02 03070, filed on March 12, 2002. (PTX 5; PTX 47)

69. The '044 patent is a divisional of U.S. Patent Application No. 11/494,693, filed on July 28, 2006 and issued as the '181 patent, which is a continuation-in-part of Application No. 10/937,612, filed on September 10, 2004 and issued as the '377 patent, which is a continuation of PCT Application No. PCT/EP03/03246, filed on March 12, 2003. (PTX 5; PTX 47)

70. The '044 patent is terminally disclaimed to the '377 patent and U.S. Patent No. 7,642,288 and U.S. Application Nos. 12/437,008 (which issued as the '060 patent), 12/591,343, and 12/902,972. (PTX 5; PTX 47)

71. The '044 patent is currently owned by Galderma Research & Development, S.N.C. and expires on March 12, 2023. (PTX 19; D.I. 287, Exh. 1, Uncontested Fact 47)

72. Galderma asserted at trial that Tolmar infringes claims 40 and 41 of the '044 patent, and Tolmar has conceded infringement of those claims. (Tr. at 53:14-17)

II. FINDINGS OF FACT RELEVANT TO OBVIOUSNESS

A. State of the Art of Acne Treatment

73. Acne is one of the most common skin diseases, affecting almost 80% of adolescents and young adults. (DTX 520 at S2; PTX 231 at 242)

74. In the field of dermatology it is recognized that, when treating a patient with acne, a pharmaceutical composition or treatment method must not only reduce the number of acne lesions and their severity, but must also be well-tolerated by the patient, in order to actually be

useful or effective for the treatment of acne. (PTX 209 at S1; Tr. at 1376:25-1377:7; 1399:20-21)

75. This tolerability component of a treatment is particularly important because acne treatment is not temporary, but rather may last for years. (*See* Tr. at 1186:15-1187:14) Additionally, the patient population most affected by acne (adolescents and young adults) tends not to be very tolerant of cutaneous side effects caused by many topical products, such as erythema, dryness, peeling, scaling, and other cutaneous irritation. (*See* Tr. at 1187:6-17)

76. Poorly tolerated side effects often lead to non-compliance, and a pharmaceutical composition cannot be useful or effective for the treatment of acne if patients refuse to use it. (PTX 209 at S1; Tr. at 1376:25-1377:7)

77. All of the clinical experts in the case have indicated that tolerability and efficacy are intertwined. Dr. Orlow stated that if side effects cause a patient to cease treatment, it "defeats the whole purpose and renders a treatment not useful, because you can't then treat the patient by not putting on the medicine." (Tr. at 1203:14-18) Dr. Thiboutot stated that "something can't be efficacious unless somebody is actually able to tolerate it and use it." (Tr. at 1399:20-21) Defendant's expert, Dr. Maibach, agreed that "the tolerability of a medication is an important consideration in patient compliance" and that "compliance is important in determining a drug's efficacy." (Tr. at 1082:13-18)

78. Good tolerability of a composition, *e.g.*, its ability to minimize side effects, is therefore an important aspect of the medication that reasonable physicians consider when treating acne patients. (PTX 209 at S1)

B. The Use of Topical Treatments for Acne

79. As of the 2002 effective filing dates of the patents at issue, a variety of topical and systemic drugs were available that affected the pathogenesis of acne and have been used to treat

acne. (*See, e.g.*, PTX 188 at 1-2; DTX 520 at S38; PTX 280 at TOL173189-90; Tr. at 1305:18-1310:9)

80. Topical retinoids were, and are, considered first line acne therapy. (DTX 520 at S5, S8, S38)

81. Topical retinoids target comedones, which are precursors to other types of acne lesions, and also target inflammation, which significantly decreases inflammatory acne lesion counts. (DTX 520 at S5-S9; Tr. at 1310:2-9; 1371:25-1372:10) At a molecular level, it is believed that retinoids work by binding to retinoic acid receptors. (PTX 228 at S22-S23; Tr. at 1395:25-1396:19)

82. Tretinoin (Retin-A®), all-trans retinoic acid, was the first retinoid introduced for topical use, in 1971. (*See* PTX 209 at S2) Tretinoin was initially formulated in a hydroalcoholic vehicle, but skin irritation was a common complaint from patients using that formulation. (*Id.*)

83. The extent of tretinoin-induced irritation was determined to be dose related, such that the higher the concentration of tretinoin in the vehicle, the more irritation the product caused. Some patients could not tolerate an optimal tretinoin concentration because of the irritation issues arising with higher doses of tretinoin. (*See* PTX 209 at S1 ("Tretinoin-induced irritation, for example, is generally dose- and vehicle-related."); Tr. at 1193:2-14) In other words, even if a physician wanted to use a stronger tretinoin concentration to increase the efficacy in a patient, that use could be limited by the intolerability of the preparation. (*See* Tr. at 1193:6-10)

84. With tretinoin, one of the ways irritation was reduced was by decreasing the concentration of active drug in the topical formulation. One of the initial formulations of Retin-A® was the cream, which was first approved by the FDA, in 1973, at a 0.1% concentration. (*See*

Tr. at 1189:7-11.) In light of the irritation caused by the 0.1% tretinoin cream, a 0.05% tretinoin cream was later introduced, followed by a further reduction to 0.025% tretinoin cream, in 1988. (*See* Tr. at 1189:12-15)

85. Unlike tretinoin, which activates all three RAR receptors (α, β, γ), tazarotene, another retinoid, was developed as a receptor-selective retinoid. (Tr. at 1395:19-1396:19 (indicating tazarotene was approved in 1997)) It was initially thought that this receptor selectivity would yield increased tolerability (similar to that observed with adapalene). (*Id.*) In clinical practice, however, this has not been the case. (Tr. at 1396:20-23)

86. As stated by Dr. Maibach in one of his publications, "tazarotene is thought to be the most irritating of the topical retinoids," causing itching, burning, irritation, and erythema. (PTX 212 at 358) In one study, "half of the patients applying tazarotene for only 2 to 10 minutes daily reported local skin irritation." (PTX 212 at 358)

87. As with tretinoin, increased concentrations of tazarotene were considered to be effective but also to lead to increased irritancy. (*See* PTX 209 at S3 ("A dose-response relationship was noted for both efficacy and tolerability [for tazarotene].")

C. Galderma Selects Differin® 0.1% as the Optimal Dose for Acne Treatment

88. Before 2002, the 0.1% concentration of adapalene was considered the "optimal concentration for efficacy and safety." (PTX 228 at S21 (figure 7); PTX 163 at S119, S121, S124) Prior to 2002, despite extensive work and publications regarding adapalene, there are no references describing testing of any dosage above 0.1% for the treatment of acne. (*See* Tr. at 1226:3-7; 1298:22-1299:14; *see also* Tr. at 873:11-23 (Dr. Potts admitting that nobody had tested anything above 0.1% adapalene in the treatment of acne as of 2001))

1. Shroot Patents: '720 Patent (1988), '895 Patent (1992), and '440 Reissue Patent (1993)

89. The Shroot patents disclose a general chemical formulation that "could result in hundreds, if not thousands of different compounds" to treat a broad range of diseases, in different dosage forms, administered in many different ways to the body, across a broad range of concentrations. (*See* Tr. at 1276:22-1277:8; 883:6-887:20) From this large genus of potential treatments, Galderma selected 0.1% adapalene as the concentration of adapalene with which to begin development of a topical treatment for acne. Dr. Shroot testified that, at the time of the Shroot patents' disclosure, the 0.1% dose was considered an optimal dose for adapalene formulations. (*See* Tr. at 1841:18-23)

2. Verschoore (1991)

90. In 1991, Galderma published its first study on use of adapalene in acne patients as Verschoore et al., *Efficacy and Safety of CD 271 Alcoholic Gels in the Topical Treatment of Acne Vulgaris*, 124 British J. of Derm. 368-71 (1991) ("Verschoore (1991)"). (PTX 244)

91. The Verschoore (1991) article reports the results of a *Phase II* clinical trial where 0.03% and 0.1% adapalene formulations, as well as 0.025% tretinoin, were tested on the faces of patients with acne. Improvements in acne and tolerability were evaluated. (*See* PTX 244 at TOL173195; Tr. at 1229:4-8)

92. The results of this study suggest that increasing the concentration of adapalene beyond 0.1% would result in significantly increased irritation. (*See* Tr. at 1230:15-20)

93. The 0.1% adapalene formulation is reported as generally causing increased irritation compared to the 0.03% adapalene formulation. (*See* PTX 244 at TOL173197)

Table 2. Mean skin safety scores at week 1 in each treatment group

	0·03% CD 271 (n=24)	0·1% CD 271 (n=24)	0·025% Tretinoin (n=24)
Erythema	1·0±0·1	1·3±0·2	1·0±0·2
Scaling	0·6±0·2	1·3±0·2	0·8±0·1
Pruritus	0·1±0·1	0·1±0·1	0·1±0·1
Burning	1·3±0·1	1·8±0·2	1·4±0·2
Dryness	0·0	0·4±0·1	0·0

(PTX 244 at TOL173197, Table 2) In reviewing Table 2, Dr. Orlow noted that "what you can see if we look at the two columns for the .03 percent adapalene and the 0.1 percent adapalene is that for a number of measures, there are notable increases in the local irritation score." (Tr. at 1229:18-21.)

94. As Dr. Orlow testified, one of ordinary skill in the art would view this data comparing 0.03% adapalene to 0.1% adapalene as suggesting a "significant increase in tolerability measures" would result from a further tripling of the adapalene dose from 0.1% to 0.3%. (Tr. at 1230:15-20)

3. Alirezai (1996)

95. The trend of increased irritation between the 0.03% and 0.1% dosages disclosed in Verschoore (1991) was later confirmed in the same dosages in aqueous gels in a publication by Alirezai et al., entitled "Comparative Study of the Effectiveness and Tolerance of 0.1 and 0.03 Percent Adapalene Gels and of a 0.025 Percent Tretinoin Gel in the Treatment of Acne," 123 Ann. Dermatol. Venereol. 165-170 (1996) ("Alirezai (1996)"). (PTX 162) This article was considered by the patent Examiner in connection with all of the patents-in-suit. (*See* PTX 1-5)

96. The Alirezai article discloses a Phase II dose-ranging study conducted on 0.03% adapalene gel, 0.1% adapalene gel, and 0.025% tretinoin. (DTX 207 at TOL175384; Tr. at 974:24-975:3, 982:2-10) The article concludes that the "study demonstrates the effectiveness of

adapalene in the topical treatment of acne, with the presence of a dose effect between the concentrations of 0.03 and 0.1%." (DTX 207 at TOL175388)

97. These data, like the data from the study described in Verschoore (1991), describe the results of a *Phase II* clinical trial with 0.03% adapalene, 0.1% adapalene, and 0.025% tretinoin gels. This study, conducted on the faces of acne patients, demonstrates that the tolerability of the 0.1% dosage was different than that of the 0.03% dosage. (*See* PTX 162 at 168-69)

98. With regards to burning, *severe* burning was seen in no patients treated with the 0.03% adapalene, but was seen in 13% of patients treated with the 0.1% adapalene aqueous gel. (*See id.* at 168) Additionally, significantly higher levels of "average" burning and itching after application were observed with the 0.1% formulation as compared to the 0.03% formulation. (PTX 162 at 168; Tr. at 1096:8-1097:18) Statistically higher levels of average persistent burning occurred with the 0.1% formulation as opposed to the 0.03% formulation. (*See* PTX 162 at 169; Tr. at 1098:7-17)

4. Allec and Verschoore (JAAD Supplement, 1997)

99. In a June 1997 supplement to the Journal of the American Academy of Dermatology (Volume 36, Number 6, Part 2), multiple articles were published that discussed "Adapalene: A novel topical retinoid receptor agonist for acne." (DTX 155 at TOL011449; *see* Tr. at 1211:2-6) Within this supplement were two articles: one written by Allec et al., which discloses how 0.1% adapalene was considered the "optimal concentration for efficacy and safety" and which was considered by the Examiner during the prosecution of the patents-in-suit (*e.g.*, PTX 1-5), and one written by Verschoore et al., which describes cumulative irritation testing on the backs and forearms of healthy subjects, including the testing of a 0.3% adapalene

concentration. Both articles were understood to have been associated with Galderma at the time of the publication. (*See* PTX 163 at S119; DTX 155)

100. As both Dr. Orlow and Dr. Maibach testified, at the time this supplement was published, it was understood by those of ordinary skill in the art that no other group anywhere in the world had more experience with adapalene than the group at Galderma. (*See* Tr. at 1156:11-14; Tr. at 1206:20-1207:4)

a. Allec (1997) Indicates to One Of Ordinary Skill in the Art That Galderma Considered 0.1% Adapalene as the Optimal Concentration

101. The Allec article, *Skin Distribution and Pharmaceutical Aspects of Adapalene Gel*, 35(6), J. Am. Acad. of Dermatol. S119-S125 (1997), teaches away from increasing the concentration of adapalene to treat acne, because it indicates 0.1% is the optimal concentration for the topical treatment of acne. (PTX 163 at S119, S121, S123; Tr. at 1205:28-1206:19) The Allec article was considered by the PTO during the prosecution history of the asserted patents. (*See, e.g.*, PTX 1-5)

102. The Allec article states:

> Our objective was to develop a formulation ***optimized for the topical treatment of acne*** by enhancing the concentration of active ingredient at the site of action to diminish local and systemic side effects and taking into account patient compliance. We describe the results of in vivo models used to select ***the optimal concentration*** of adapalene for efficacy and safety, the skin distribution profile of the drug after topical application of ***adapalene 0.1% gel***, the concept of targeted delivery to the pilosebaceous unit, and finally the composition of ***adapalene 0.1% gel***.

(PTX 163 at S119 (emphasis added))

103. A person of ordinary skill in the art would have recognized these statements as a conclusion of the company that developed adapalene had determined, from all the data it had on

hand, that 0.1% was the optimal concentration for acne treatment, balancing efficacy and safety. (Tr. at 1206:10-19)

104. The Allec article further included a section under the heading "Selection of The Optimal Concentration of Adapalene For Efficacy And Safety," describing efficacy studies performed in the Rhino mouse model and irritation studies completed in the rabbit irritation model. (PTX 163 at S121-22) That section concluded: "Based on these in vivo results, 0.1% was considered as the optimal concentration of drug for adapalene gel. ***This choice was subsequently confirmed in clinical trials of safety and efficacy***." (PTX 163 at S123 (emphasis added))

105. A person of ordinary skill in the art would understand this statement to reference clinical trials in humans. (*See* Tr. at 1209:6-8)

106. This statement also demonstrated to one skilled in the art that Galderma had carried out the dose-response curve and had determined that 0.1% was the optimal dose for the treatment of acne, particularly in light of the results of the clinical trials set forth in the Verschoore (1991) and Alirezai (1996) articles. (*See* Tr. at 1209:21-1210:5; 1211:2-20) One of ordinary skill would understand those Phase II studies, which discouraged increasing the adapalene dosage beyond 0.1%, to support the statements in the Allec article regarding how the 0.1% adapalene concentration yields the optimal "balance of efficacy and tolerability." (Tr. at 1235:23-1236:22)

b. Verschoore (1997) Confirms to One of Ordinary Skill in the Art That Galderma Considered 0.1% Adapalene as the Optimal Concentration

107. Ten pages from Allec in the same supplement is another article, entitled Verschoore, et al., *Adapalene 0.1% Gel Has Low Skin Irritation Potential*, 36(6) J. Am. Acad. of Dermatol. S104-109 (1997) ("Verschoore (1997)"). (DTX 155) This article discusses the results

of Phase I clinical trials conducted by Galderma on either the backs or forearms of healthy volunteers. (*See* DTX 155 at TOL11449-55)

108. The focus of the article is a discussion of the results of two Phase I studies (studies A and B), which compared adapalene 0.03%, adapalene 0.1%, and 0.025% tretinoin gel. (DTX 155 at TOL11449-54) There is one line of data on a chart in the article that indicates that 0.3% adapalene gel had been tested, as well as an apparent reference in the introduction of the article. (*See* DTX 155 at TOL011450, TOL011452-53, at Table I (Row 4))

109. Based predominantly on the results of studies A and B, the article concludes that "[a]dapalene aqueous gel 0.1% was well-tolerated when applied topically in standard cumulative irritation tests." (DTX 155 at TOL011454) It also states that "[t]he lower degree of skin irritation in clinical use has been confirmed in trials in acne patients in whom equal or superior efficacy to a tretinoin gel was demonstrated" and cites to references 4 and 5. (*Id.*) These two references also specifically disclose studies of *0.1% adapalene gel.* (*See* Tr. at 895:2-17 (Dr. Potts confirming references 4 and 5 do not discuss 0.3% adapalene))

110. Accordingly, Verschoore (1997) demonstrates that Galderma decided to pursue and obtain clinical approval for *0.1% adapalene.* Further, the mention of the 0.3% concentration in the article demonstrates to one skilled in the art that the 0.3% adapalene was tried and *rejected* as the dosage to pursue for further clinical testing. (*See* Tr. at 1227:21-1228:6; 1211:2-21)

5. Czernielewski (2001)

111. In 2001, Galderma published another paper by Czernielewski, et al., entitled "Adapalene Biochemistry and the Evolution of a New Topical Retinoid for Treatment of Acne," 15 (Suppl. 3) J. Eur. Acad. Dermatol. Venerol. 5-12 (2001), a review article that summarized the findings of other adapalene 0.1% studies, including Alirezai (1996) and Verschoore (1997).

(PTX 177) The Czernielewski article was considered by the patent examiner in all of the Galderma patents-in-suit. (*See, e.g.*, PTX 1-5)

112. The Czernielewski article discloses that the "primary objective in the development of adapalene was to create a topical agent with retinoid therapeutic effects that is considerably less irritating than topical tretinoin." (DTX 21, DTX 21A at GAL0022189) The article further states that "adapalene is a very well tolerated compound with markedly lower irritation potential as compared with tretinoin." (DTX 21, DTX 21A at GAL00022189)

113. The Czernielewski article suggests that 0.1% adapalene is the optimal dose for the treatment of acne. It states: "Adapalene 0.1% became the standard concentration for subsequent adapalene formulations." (PTX 177 at TOL171093) Notably, in making this statement, the Czernielewski article cites to the Phase II study in the Alirezai (1996) article (PTX 162) as reference 20. (*See* PTX 177 at TOL171093, TOL171095)

114. The Czernielewski article does not disclose any information about any doses higher than 0.1% adapalene. (*See* Tr. at 874:23-24) Dr. Potts conceded that the Czernielewski article does not speak to 0.3% adapalene at all. (*See* Tr. at 874:23-24)

6. Differin® 0.1% Gel Data Sheet (1996)

115. The Differin® Gel, 0.1% product insert ("the Differin® 0.1% Gel Data Sheet") contains a section entitled "Overdosage," which states: "OVERDOSAGE: DIFFERIN® Gel is intended for cutaneous use only. *If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur.*" (PTX 255 at TOL 171086)

D. The Prior Art Taken as a Whole Does Not Motivate One of Ordinary Skill in the Art to Develop a 0.3% Adapalene Formulation

116. Based on prior experience with tretinoin and tazarotene, the person of ordinary skill in the art would have had a reasonable expectation that tripling the concentration of adapalene to 0.3% would increase the incidence and severity of side effects compared to the 0.1% concentration. (Tr. at 1256:7-1257:4) If one were to modify the 0.1% formulation to be a 0.3% formulation, one would have expected a clinically meaningful increase in the incidence and severity of irritation. (*See* Tr. at 1256:7-1257:4 (Dr. Orlow indicating "there was expectation on the part of one of ordinary skill in the art that tripling the concentration was going to cause a significant increase in tolerability issues"))

117. In March 2002, general experience with topical acne medications tended to show that dose and irritation correlated. (PTX 209 at S1) The experience in the art, thus, taught away from increasing the concentration of adapalene to obtain a product with a still-favorable tolerability profile.

118. In allowing the asserted patents, the Examiner indicated: "the present claims require the effective use of 0.3% of adapalene, and applicant has shown through unexpected results that the particular dosage of 0.3% adapalene was more effective than 0.1% adapalene in treating acne lesions while minimizing side effects, and Shroot in view of Differin® Gel Data Sheet does not render obvious the use of 0.3% adapalene as disclosed." (PTX 36 at 5-6)

E. None of the Art Cited by Tolmar Establishes the Obviousness of the Claimed Invention

119. A person of ordinary skill in the field of the asserted patents is a person with an advanced degree (an M.D. or a Ph.D. in clinical pharmacology or a related field) and several years of experience either as a dermatologist treating skin diseases with topical medications, or

as a clinical researcher designing clinical trials or evaluating results of clinical trials of topical formulations for the treatment of dermatological disorders. (*See* Tr. at 1180:4-12)

120. Tolmar contends that each of the asserted claims of the patents-in-suit would have been obvious to a person having ordinary skill in the art at the time of invention. Specifically, Tolmar contends that the asserted claims would have been obvious over the following combinations of references:

- Differin® 0.1% Adapalene Gel/Data Sheet in combination with any of Verschoore (1997) and/or the Shroot patents and/or Goldfarb (2000) and/or Euvrard (2002);
- Verschoore (1997) alone or in combination with the Differin® 0.1% Adapalene Gel/Data Sheet; and
- The Shroot patents alone or in combination with any of Verschoore (1997) and/or Czernielewski (2001) and/or Goldfarb (2000) and/or Euvrard (2002) or further in combination with the Differin® 0.1% Adapalene Gel/Data Sheet.

121. None of these references, alone or in combination, provide sufficient motivation or reasonable expectation of success for a person of ordinary skill in the art to develop a 0.3% adapalene formulation for the treatment of acne.

1. The Shroot Patents

122. U.S. Reissue Patent No. RE 34,440 to Shroot ("the '440 reissue patent") (DTX 152) is a reissue of the Shroot U.S. Patent No. 5,089,895 ("the '895 patent") (PTX 156), which is a divisional of the Shroot U.S. Patent No. 4,940,696, which is a divisional of the Shroot U.S. Patent No. 4,717,720 ("the '720 patent") (PTX 155), which issued on January 5, 1988 (collectively, "the Shroot patents"). As the Shroot patents are in the same patent families, their specifications are nearly identical. (*Compare* DTX 152, *and* PTX 155, *with* PTX 156)

a. The Broad Disclosure of the Shroot Patents Provides No Motivation or Suggestion to Select 0.3% Adapalene for the Treatment of Acne

123. As stated by Dr. Orlow, the Shroot patents disclose a "prototypic structure, which, with the various R groups, varied, could result in hundreds, if not thousands of different compounds. That could be used to treat a broad range of conditions . . . administered in many different ways to the body . . . across a broad range of concentrations." (Tr. at 1276:22-1277:8) There is nothing in the Shroot patents that directs one of ordinary skill in the art to a gel containing 0.3% adapalene for the treatment of acne. (*See* Tr. at 1277:20-1278:1)

124. Not only do the Shroot patents disclose a broad range of chemical compounds, but the Shroot patents further disclose broad dosage ranges of the potential active ingredients and in different types of formulations:

> The topical or ocular composition contains preferably between 0.0005 and 5 weight percent of the active compound based on the total weight of the composition. . . . The concentration of the compound(s) of Formula I in the cosmetic compositions is between 0.0005 and 2 weight percent, preferably between 0.01 and 1 weight percent, based on the total weight of the composition.

(DTX 152 at 6:3-6, 6:19-22)

125. Dr. Shroot described the "range of doses" tested in the rabbit irritation test of the patents was "a vast data set." (Tr. at 1841:12-17)

126. The range of 0.0005% to 5% for topical compositions covers four orders of magnitude (or a 10,000-fold dosage range). (Tr. at 1277:13-19) The range of .0005% to 2% for cosmetic compositions covers a 4,000-fold range. (*Id.*; Tr. at 886:24-887:8) Even the "preferred" range of 0.01% to 1% is a hundred-fold dosage range. (Tr. at 887:9-20; 1277:13-19)

127. Several of the examples in the Shroot patents disclose adapalene topical formulations. Example A and Example E disclose the low dose of 0.001% adapalene, and

Example D discloses the highest disclosed dose of 0.1% adapalene. (*E.g.*, PTX 155 at 16:43, 17:23, 17:29-31, 17:36) There is nothing in the Shroot patents that specifically suggests selecting 0.3% adapalene out of those broad ranges. (Tr. at 1277:23-1278:1)

128. Furthermore, the Shroot patents indicate the claimed compounds can be used in a wide range of applications, including "systemic treatment" of dermatological diseases (acne in addition to other keratinization disorders), dermatological diseases with inflammatory and/or immunoallergic components, atopy (cutaneous or respiratory), and ophthalmology. (*See, e.g.*, PTX 155 at 1:8-22, 4:53-5:4)

129. The Shroot patents indicate the resultant compositions may be administered in a number of different ways, including enterally (tablets, gelules, lozenges, syrups, suspension, solutions, powders, granules, or emulsions), parenterally (solutions or suspensions for perfusion or injection), topically, or ocularly. (*See, e.g.*, PTX 155 at 5:26-33)

130. The Shroot patents further indicate that there are a number of different composition types capable of topical administration, such as ointments, tinctures, creams, pomades, powders, impregnated pads, buffers, solutions, lotions, gels, sprays, and suspensions. (*E.g.*, PTX 155 at 5:34-42) Dr. Potts indicated that this is a "large number" of different topical applications. (*See* Tr. at 886:3-17)

2. Verschoore (1997)

131. The Verschoore (1997) article is entitled "Adapalene 0.1% gel as low skin-irritation potential," and lists co-inventor Janusz Czernielewski as a co-author. (DTX 155) Verschoore (1997) was not cited to or considered by the U.S. Patent Office during prosecution of any of the patents-in-suit.

132. There is a table in Verschoore (1997) that reports some of the results of thirteen different Phase I studies undertaken by Galderma "in 339 healthy human volunteers to

investigate the cutaneous safety of adapalene (Table I)." (DTX 155 at TOL11450) One of the thirteen studies involved testing 0.3% adapalene on the *back* of 25 *healthy individuals* compared to a vehicle. (*Id.* at TOL11452-53 at Table I (Row 4)) There is a single row in the table reporting some data from this study that appears to be referenced in the introduction of the article. (*See id.* at TOL11450) This line of data shows that 0.3% adapalene performed well in the occlusion test on the back of healthy individuals.

133. The Phase I irritation test described in Verschoore (1997) was a screening test done on uncompromised healthy skin on the back as a prelude—not a substitute—to clinical testing on the face or on patients with disease. (*See* DTX 155 at TOL011454 (describing skin irritation model as "pharmacologic model" for skin penetration or biologic activity); Tr. at 1099:25-1100:8; 1794:7-1795:23; 1225:21-24 (Dr. Orlow indicating that success in Phase I does not necessarily predict success in subsequent clinical testing)) It was conducted using the repeat insult patch test (RIPT), which applies the tested products under occlusion on the backs of healthy individuals and not on facial skin afflicted with acne. (*See* DTX 155 at TOL011452)

134. Thus, the purpose of the Phase I studies reported in the Verschoore (1997) article was to establish that the drug was safe enough to proceed to Phase II and III clinical trials in patients with the disease. (*See* Tr. at 1242:10-20 (Dr. Orlow describing the cumulative irritation test as a "gating step")) A skilled person would understand that data from these Phase I studies conducted in healthy skin *cannot* be extrapolated to how the product will work in acne patients. (Tr. at 1796:15-1797:12 (Dr. Czernielewski testified, "[Y]ou cannot extrapolate from those tests to what will happen in [a] given patient population."))

135. A skilled person would understand that "[r]esults obtained via patch-testing methods that involve application to the back cannot be assumed to reliably predict facial

irritation." (PTX 205 at S17) As Dr. Orlow testified, a skilled person would know that patch testing on the backs of healthy volunteers is a "poor predictor" of the irritation experienced by facial skin damaged by acne. (Tr. at 1244:19-1245:6)

136. Even Dr. Maibach had previously written that the 21-day cumulative irritation test "had ***failed*** to predict adverse reactions to skin ***damaged by acne*** or shaving, or ***sensitive areas such as the face***." (PTX 165 at 49-50 (emphasis added))

137. Those of ordinary skill in the art would have known that applying a product on the back under occlusion is very different from application of the product to inflamed lesions on the patient's face in the clinical setting. (*See* Tr. at 1242:21-1243:3; 1796:6-1797:4) As Dr. Czernielewski testified, those of ordinary skill would also know that back skin and forearm skin are thicker and less sensitive than facial skin, which is "more thin, more delicate, and . . . [has] more inflammatory response." (Tr. at 1796:10-14)

138. The type of testing performed on the back under occlusion did not permit the assessment of elements of the retinoid reaction typically evaluated in clinical practice, such as stinging and burning, itching, dryness, or scaling. (Tr. at 1102:16-1104:19)

3. Galderma's IND and Other Internal FDA Documents

139. In the course of developing 0.3% adapalene formulations, Galderma conducted several studies, the results of which were submitted to the FDA in seeking regulatory approval.

140. For example, Galderma generated a protocol for a pharmacokinetic study—study 2649—on March 16, 2000. (DTX 607, Vol. 1.15 at GAL000004787; Tr. at 365:13-25) This study investigated the pharmacokinetics of adapalene 0.3% gel following repeated topical administration for 10 days in 8 subjects with mild to moderately severe acne and monitored local tolerability of the product. (DTX 607, Vol. 1.15 at GAL000004780) The results of this study, conducted in *acne patients*, were reported in the patents-in-suit and also incorporated into

Galderma's Investigational New Drug Application ("IND"). (*See, e.g.*, PTX 1 at 4:60-5:30; DTX 607, Vol. 1.15 at GAL000004719, GAL000004779-86; Tr. at 364:23-365:12; 525:9-526:1; 526:7-21; 552:22-554:25) Dr. Czernielewski, one of the named inventors, was responsible for the review and evaluation of all the information contained within Galderma's IND, including the 2649 study. (PTX 481 at GAL000005492-94; Tr. at 594:24-595:25; 602:18-24)

141. The introduction of the protocol for study 2649 states, "Preliminary studies in healthy Subjects (ref 1 and 2) show that the 0.3% concentration is likely to be only slightly more irritant than the 0.1% concentration." (DTX 607, Vol. 1.15 at GAL000004799; *see also* DTX 607, Vol. 1.15 at GAL000004842, GAL000004879, GAL000004957) This statement is made with regard to ***healthy*** subjects and is not predictive of the irritation of 0.3% adapalene compared to 0.1% adapalene in acne patients. (Tr. at 366:25-367:16; 382:9-383:19; *see also* Tr. at 387:4-388:19)

142. The preliminary results for study 2649 were available to Galderma by August 1, 2000. (DTX 607, Vol. 1.15 at GAL000004779) This study demonstrated the following: "*The overall local tolerance of subjects to the treatment was good.* Dryness and scaling occurred on the face in all subjects with a peak (score of 2 - moderate) at Day 7. These symptoms decreased slowly after the end of treatment. All 8 subjects experienced transient stinging/burning sensations immediately after treatment application." (DTX 607, Vol. 1.15 at GAL000004719 (emphasis added); *see also* GAL000004779-86) This information is very similar to the information presented in the patents. (*See, e.g.*, PTX 1 at 5:21-30; *see* Tr. at 553:16-554:16)

143. Galderma submitted its IND application to conduct the Phase II clinical trial in the U.S. for Adapalene Gel, 0.3% on October 2, 2000. (DTX 607, Vol. 1.1 at GAL000000002; Tr. at 304:21-24) Pursuant to FDA regulations, Galderma was required to submit all studies

Galderma had ever conducted using the 0.3% adapalene concentration to the FDA. (Tr. at 409:17-22; 552:22-553:15) The IND, thus, included studies Galderma had conducted with 0.3% adapalene on healthy subjects (Studies 19027, 2644, 2645, 2646, and 2017) and subjects with photodamaged skin (Studies 2506 and 9305). (*E.g.*, DTX 607, Vol. 1.1 at GAL000000043-48) The IND also included the preliminary results of Galderma study 2649, discussed above. (DTX 607, Vol. 1.15 at GAL000004719, GAL000004779-86; Tr. at 547:24-549:13)

144. On October 4, 2001, Galderma submitted to the FDA its End of Phase 2 Meeting Request and Briefing Package that contained results from pharmacokinetic Study 2649 and the Phase II study that are mirrored in the patents-in-suit. (*See* PTX 320A at GAL000006751, GAL000006812-14, GAL000006818-22; Tr. at 575:11-583:8; *e.g.*, *compare* PTX 320A at GAL000006812-14, *with* PTX 1 at 4:60-5:30; *compare* PTX 320A at GAL000006818, *with* PTX 1 at 2:4-9, 4:49-58, 6:10-15; *compare* PTX 320A at GAL000006819-20, *with* PTX 1 at Figs 1-3; *compare* PTX 320A at GAL000006821, *with* PTX 1 at 5:31-6:5; *compare* PTX 320A at GAL000006822, *with* PTX 1 at 2:4-9, 6:10-15) Dr. Graeber and Dr. Czernielewski were involved in preparing the Briefing Package and participated in the End of Phase 2 meeting with the FDA. (Tr. at 575:11-576:18)

145. The Briefing Package specifically noted the surprising and unexpected results of the Phase II trial that confirmed the results of the PK study 2649. The Briefing Package stated that *"[a]s expected* there was a higher incidence of adverse events with the 0.1% and the 0.3% concentrations (54.3% and 51.4%, respectively) compared to the gel vehicle (40.5%)." (PTX 320A at GAL000006821) But the Briefing Package states in the very next sentence: "*However*, the incidence of adverse events was comparable with the two active concentrations. In

particular, the incidence of local adverse events related to local tolerability was comparable with the two active concentrations (see Table below)." (*Id.*)

146. Dr. Graeber testified that these observations from the Phase II study were "very encouraging" and led Galderma to conclude that 0.3% adapalene was more effective than 0.1% adapalene and well-tolerated:

> Well, this was, of course, very—very encouraging for us. The . . . point was that adapalene 0.1 percent was regarded to be optimized, the best tolerated retinoid.
>
> People who . . . had experienced an increase in concentration, an increase in dose, would . . . increase significantly the retinoid dermatitis. And so the . . . gain in effectiveness with a higher concentration would be . . . impacted by an increase of more severe irritation. So that ultimately, the benefit/risk of higher concentrations would not be . . . positive.
>
> And here we have a situation where we had an effect and we had good tolerability. So that basically led us to conclude that we had the product that was more effective than 0.1 percent, well tolerated, so that we could take it into Phase III and fully develop it to submission, basically the evidence from Phase II with the Phase III study, and then sort of take this as a basis of the submission.

(Tr. at 580:2-581:25)

147. Likewise, Dr. Czernielewski repeatedly testified at his deposition that he was "surprised" by the results of the Phase II trial, which demonstrated the 0.3% adapalene formulation was highly effective but possessed a tolerability profile comparable to the 0.1% formulation:

> The basis for surprise is that this beneficial effect, efficacy-wise, is not follow[ed] with the dramatic worsening of the tolerance. That's what is the *major surprise* and—and innovation of this molecule, which is adapalene. . . . [I]n our experience, in medical experience, in clinical experience, it is [a] well-known fact that these other products, tretinoin, tazarotene, you have severalfold increase of the number of either severe events, appearance of quite severe adverse events, very often there is a need to change to

> pausality in the administration of the product, and of the patient quit treatment because they cannot support this higher concentration.

(Tr. at 1804:23-1805:21)

4. Photodamage and Actinic Keratosis Articles (2000)

a. The Goldfarb References (2000)

148. Tolmar relies on an article, Goldfarb, *Using Adapalene to Treat Photodamage*, Supp. to Skin & Aging 4-7 (Nov. 2000) (DTX 161, "Goldfarb Article"), and an abstract, Goldfarb et al., *Photographic Assessment of the Effects of Adapalene 0.1% and 0.3% Gels and Vehicle on Photodamage Skin*, 14 (Supp. 1) J. Eur. Acad. Dermatol. Venerol. 315 (2000) (PTX 185, "Goldfarb Abstract"), which examine the treatment of photodamaged skin with adapalene, to support its contentions that the use of 0.3% adapalene gel to treat acne was obvious. The Goldfarb Abstract was considered by the Examiner during prosecution of the asserted patents; the Goldfarb Article was not. (Tr. at 865:20-22; Tr. at 745:23-746:1) The Goldfarb Article and the Goldfarb Abstract describe the same single clinical study ("the Goldfarb study"), and, accordingly, will be addressed together. (Tr. at 866:6-867:7) Dr. Goldfarb testified that he did not recall writing the article. (Tr. at 1827:6-1828:10; 1828:23-1829:8 (discussing DTX 161).)

149. In the Goldfarb study, 90 Caucasian patients in their mid-60s, mostly male and many of whom were farmers, all with actinic keratosis, were split into three groups and treated with 0.1% adapalene, 0.3% adapalene, or vehicle. (DTX 161 at 4-5) Based on the results of the study, the authors described both adapalene gel concentrations as being "tolerated well." (DTX 161 at TOl172907) The authors stated that adapalene "could be an alternative for a patient with photoaged skin who . . . is looking for gentle therapy." (DTX 161 at TOL172904)

150. Actinic keratosis/photodamaged skin is not analogous to acne skin. (*See* Tr. at 912:15-18) As Dr. Orlow testified, "they're totally different disorders." (Tr. at 1289:19-1290:1)

Therefore, the results of clinical studies performed on patients with photodamaged skin are not predictive of how the same drug would affect patients with acne. (*See* Tr. at 315:16-23) One of ordinary skill in the art would know that these results on photodamaged skin should ***not*** be extrapolated to acne. (*See* Tr. at 317:4-12)

151. As stated by Dr. Orlow, the patient populations are also fundamentally different. (Tr. at 1290:5-11) Because actinic keratosis/photodamage occurs as a result of excessive exposure to UV radiation, it is more common in patients with lighter skin types who have a history of chronic sun exposure. (*See, e.g.*, DTX 161 at 5 ("All the subjects in the sample were Caucasian.")) Acne, however, can affect individuals of all skin types. (Tr. at 1286:21-1287:1)

152. Additionally, patients with acne are generally young, mostly adolescents and young adults. (*See* DTX 520 at S2) Patients with photodamaged skin—due to the requisite decades of chronic sun exposure—are on average much older than acne patients; their skin is often, thicker, drier, and less irritable. (Tr. at 1286:11-24; 1288)

153. In contrast to the skin of younger acne patients, the skin of older patients with photodamaged skin can tolerate, and may even require, higher doses of retinoids. (*See* PTX 186 at GAL000248161)

154. Dr. Maibach has published multiple articles on this issue. (*See, e.g.*, PTX 182 at 32 ("Inflammatory response to an exogenous agent declines in people over 70 years old. The inflammatory response is slower and less intense, and some clinical signs of skin damage are absent . . . . The manifestation of skin irritation is blunted."); PTX 211 at 1017 ("Thus, compared with young skin, the skin of older subjects reacts more slowly and with less intensity to both primary irritants and allergens.")) Dr. Maibach's publications and the literature cited above show that one of ordinary skill in the art would understand older skin with photodamage

and actinic keratoses to be less sensitive to the retinoid reaction compared to younger skin with acne.

b. Euvrard (2002)

155. Tolmar is also relying on an article authored by Euvrard, entitled "How Adapalene Can Treat Actinic Keratoses," Supp. to Skin & Aging 12-15 (Nov. 2000). (DTX 163) The Euvrard article was not cited to nor considered by the U.S. Patent Office during prosecution of any of the patents-in-suit. (PTX 1-5, Tr. at 748:18-21)

156. The Euvrard article discloses a study using adapalene 0.1% and 0.3% to treat photodamaged skin, and in particular contralateral actinic keratoses on the hands and forearms of organ transplant patients who were presumably on immunosuppressive drugs. (DTX 163 at TOL172889; Tr. at 749:3-8) The authors concluded, "[t]olerance was excellent everywhere" and "[t]aking into account the good tolerance of adapalene, these results encourage further studies on the use of adapalene at . . . higher dosage regimens." (DTX 163 at TOL172890, TOL172892, Tr. at 749:9-18)

157. Differences exist between the properties of facial skin and skin on the extremities, such as the hands and forearms studied in Euvrard. Facial skin, more traditionally afflicted with acne, is much more prone to irritation and often thinner than skin on the extremities. (Tr. at 918:10-16)

158. Based on these differences, one of ordinary skill in the art would not conclude from Euvrard that adapalene 0.3% gel would result in the same tolerability profile in patients with acne vulgaris. (*See* Tr. at 1297:17-1298:21; *see also* Tr. at 919:16-18 (Dr. Potts admitting that Euvrard does not suggest further studies in treating acne))

F. Objective Indicia of Nonobviousness

1. Unexpected Results of the Clinical Studies

159. Clinical trials designed to prove the safety and efficacy of a drug are needed in order for the FDA to grant approval of a pharmaceutical drug. There are several phases of clinical trials needed in order for proper evaluation of the safety and efficacy of a drug.

160. Phase I studies assess the safety of a drug. This initial phase of testing usually includes healthy volunteers and is designed to determine the effects of the drug on humans. Success in Phase I is not necessarily predictive of success in later Phase II and III testing. (Tr. at 1225:21-24)

161. Phase II studies are designed to further gather safety data but also to begin to test the efficacy of a drug and/or examine the effects of different doses of a drug. This second phase of testing generally lasts longer than Phase I testing and involves a greater number of patients. Most Phase II studies are randomized trials in which one group of patients receives the experimental drug, while a second "control" group receives a placebo. Results from Phase II trials allow for the generation of comparative information about the relative safety and effectiveness of the experimental drug. (*See* PTX 264 at GAL0000242679; Tr. at 941:16-942:23)

162. Phase III studies involve randomized and blind testing in even larger numbers of patients than Phase II trials. Phase III studies are designed to provide further evidence of the efficacy and safety of the drug. (*See, e.g.*, PTX 307 at GAL000033765)

163. Galderma conducted a Phase II clinical study comparing the efficacy and tolerability of 0.3% adapalene gel to 0.1% adapalene gel and published the results in Pariser et al., *The Efficacy and Safety of Adapalene Gel 0.3% in the Treatment of Acne Vulgaris: A*

Randomized, Multicenter, Investigator-Blinded, Controlled Comparison Study Versus Adapalene Gel 0.1% and Vehicle, 76 Cutis 145-151 (2005). (PTX 219)

164. Safety and tolerability were assessed in this Phase II trial primarily through adverse event reporting. (Tr. at 1402:2-4) The results from the study demonstrated that adapalene 0.3% was well-tolerated, as treatment related adverse events were overwhelmingly mild and moderate, with very low dropout rates, and only two patients treated with 0.3% adapalene experienced a severe adverse event. (PTX 219 at 150; Tr. at 1402:13-1403:14)

165. Galderma also conducted Phase III clinical trials in order to obtain market approval from the FDA to sell a 0.3% adapalene product. The results of these trials confirmed that 0.3% adapalene gel was more effective than both the vehicle control and the 0.1% adapalene product. (Tr. at 1411:2-1412:3)

166. The unexpected tolerability of adapalene 0.3% gel was demonstrated by the fact that the severity of most of the reported adverse events was low and the effects were transient. (PTX 231 at 245-46, 248; Tr. at 1426:12-1427:12) Additionally, the low dropout rate due to adverse events further supports the unexpected tolerability of the 0.3% adapalene formulation. (*See* PTX 231 at 246; Tr. at 1425:13-17)

167. A sentence in the specification of the patents-in-suit states, "[f]rom this table, it is noted that the occurrence of undesirable side effects is statistically the same for the two gels with the different concentrations of active agent." (*E.g.*, PTX 3 at 6:42-45)

168. The term "statistically the same" is commonly understood to mean not statistically significantly different (PTX 203 at GAL000277257; Tr. at 1150:1-1151:4), and the "table" in the patent does show that there is no statistically significant difference between the adverse events for the 0.3% and 0.1% formulations (Tr. at 1492:2-14; 1495:11-1496:23).

169. Even with regard to the number of adverse events, the U.S. Phase III trial demonstrated that there was no statistically significant difference between the 0.3% gel and the 0.1% gel, except for dryness:

Adverse Event	0.3% Adapalene # of patients (percentage)	0.1% Adapalene # of patients (percentage)	Difference statistically significant
Erythema	2 (0.8%)	3 (1.1%)	No
Discomfort skin	15 (5.8%)	12 (4.6%)	No
Desquamation	4 (1.6%)	2 (0.8%)	No
Pruritus	5 (1.9%)	4 (1.5%)	No
Irritant Dermatitis	2 (0.8%)	2 (0.8%)	No
Sunburn	3 (1.2%)	3 (1.1%)	No
Dermatitis-contact	0 (0.0%)	1 (0.4%)	No
Dermatitis	1 (0.4%)	2 (0.8%)	No
Skin Dry	36 (14%)	17 (6.5%)	Yes
Urticaria	0	0	No
Eczema	0	0	No
Excoriation	0	0	No
Atopic Dermatitis	0	0	No

(PTX 300 Vol. 1.1 at GAL000011022)

2. Prior Art Taught Away from Increasing the Concentration of Retinoids

170. It was the general consensus in the dermatological community that increasing retinoid dosage would result in a significant increase in irritation. (*E.g.*, PTX 209 at S1) This belief was supported by comparisons of the dosages of various retinoids such as tretinoin and tazarotene.

171. Decades of experience with the use of retinoids in the dermatological community taught away from increasing the dosage of 0.1% adapalene gel, as it was generally believed that increasing the dosage of any retinoid would increase the side effects experienced by the patient.

(Tr. at 1196:19-1198:5; 1281:23-1282:11; 1299:7-19; 1256:7-1257:4; 1805:10-21; 1401:10-16; 1392:10-16)

172. Further, Verschoore (1991) and Alirezai (1996) reported that side effects were higher for the 0.1% dosage than they were for the 0.03% dosage. (PTX 244 at 370; PTX 162 at 168-69)

173. Also, Galderma had published articles indicating that it believed the 0.1% dosage was "optimal." (*See, e.g.*, PTX 163 at S121, S123; PTX 228 at S21; PTX 177 at TOL171093 ("Adapalene 0.1% became the standard concentration for subsequent adapalene formulations.")) These publications also would have discouraged any deviation from the 0.1% concentration.

3. Differin® 0.3%, Gel Is a Commercial Success

a. Differin® 0.3%, Gel Is a Success in the Marketplace

174. Since its launch in June 2007, Differin® 0.3%, Gel has been successful in the marketplace. (Tr. at 1582:10-18; 1583:25-1584:8; 1586:19-23) Differin® 0.3%, Gel was a late entry into the topical retinoid market, launching forty years after the first retinoid was introduced. (Tr. at 1586:11-18; 1585:16-1586:10) At launch, there were multiple branded and generic topical retinoids already on the market. (Tr. at 1585:3-15; 1601:6-1602:1)

175. Despite Differin® 0.3%, Gel's late entry into this crowded market, the number of Differin® 0.3%, Gel prescriptions in the U.S. has increased significantly, growing from 63,000 in the third quarter of 2007 -- its first full quarter -- to its peak of 184,000, which occurred in the fourth quarter of 2008. (PTX 122)

176. Annual Differin® 0.3%, Gel prescriptions totaled 553,000 in 2010. (*Id.*)

177. Since launch through the second quarter of 2011, there have been more than 2.1 million total prescriptions for Differin® 0.3%, Gel filled in the U.S. (*Id.*)

178. Annual Differin® 0.3%, Gel revenues totaled $96.2 million in 2010. (PTX 126) From June 2007 through June 2011, U.S. Differin® 0.3%, Gel revenues totaled $337.0 million. (PTX 126; Tr. at 1587:12-15)

179. Differin® 0.3%, Gel accounted for 4.9% of all prescriptions for topical retinoids in the third quarter of 2007 and a peak of 14.1% of all such prescriptions in the fourth quarter of 2008. (PTX 124; Tr. at 1595:15-1596:8; 1602:2-12)

180. Moreover, as Dr. Vander Veen testified, even with the inclusion of ***all prescription acne products***, including systemic/oral prescriptions, Differin® 0.3%, Gel still maintained a market share of 3.2% of well over 250 products. (Tr. at 1705:12-19)

181. Differin® 0.3%, Gel maintains a stable refill rate as well. (Tr. at 1603:14-1605:8; PTX 135) If the success of the product was due solely to marketing acumen, one would expect that the refill rate would fall substantially, rather than remain stable. (Tr. at 1603:25-1604:13)

182. The entry of a generic 0.1% adapalene gel formulation in the second quarter of 2010 does not appear to have affected consumer demand for the Differin® 0.3%, Gel product. (Tr. at 1590:20-1593:11; 1592:4-9) Differin® 0.3%, Gel captured 12.3% of all topical retinoid prescriptions in the first quarter of 2010, the quarter *before* generic adapalene's entry. Even *after* the entry of generic adapalene 0.1%, Differin® 0.3%, Gel maintained a share between 10 and 12 percent—despite a decreasing trend that started before the generic adapalene products were launched. (Tr. at 1595:15-1596:8; 1589:24-1590:12; PTX 124.)

183. Likewise, the revenues of Differin® 0.3%, Gel remained stable and were not impacted by the introduction of generic adapalene 0.1%. Conversely, Differin® 0.1%, Gel's revenues fell precipitously once generic 0.1% adapalene entered the market. (Tr. at 1592:14-1593:20; PTX 128)

184. The maintenance of market share and revenue for Differin® 0.3%, Gel cannot be explained by an increase in promotional activity. (Tr. at 1594:2-1595:14; 1617:25-1618:10)

185. The fact that Tolmar is seeking approval for its own generic form of 0.3% adapalene also indicates that Differin® 0.3%, Gel is a success in the marketplace. (Tr. at 1618:22-1619:18) As Mr. Jarosz testified, it takes time and effort to enter a business, and the fact that Tolmar is seeking to market 0.3% adapalene rather than 0.1% adapalene, which is already genericized, is "strong economic evidence" of marketplace success. (Tr. at 1619:3-12)

b. Differin® 0.3%, Gel's Marketplace Success is Due to the Patented Features and Benefits

186. There is a nexus between the commercial success of the Differin® 0.3%, Gel product and the invention disclosed and claimed in the patents-in-suit. (Tr. at 1584:9-1585:2)

187. Although generic 0.1% adapalene is now available, and Galderma's promotional spending has decreased, Differin® 0.3%, Gel's revenues continue to increase. If doctors and patients did not perceive any therapeutic differentiation between Differin® 0.3%, Gel and 0.1% adapalene, then doctors and patients would purchase the cheaper generic 0.1% adapalene gel rather than the more expensive branded Differin® 0.3%, Gel. (Tr. at 1590:20-1595:14)

III. THE ASSERTED PATENTS ARE NOT INVALID FOR LACK OF WRITTEN DESCRIPTION

A. It Was Well Known to Use Topical Retinoids as a Component of Combination Therapy to Treat Severe Forms of Acne Prior to 2002

188. The term "acne" as used in the claims of the '558 and '044 patents means a "dermatological condition selected from the group consisting of common acne, comedones, polymorphous acne, nodulocystic acne, acne conglobata, secondary acne such as solar, drug-related or occupational acne." (PTX 4-5; D.I. 290 at 5) Nodulocystic acne and acne conglobata are considered severe forms of acne. (Tr. at 937:25-938:24)

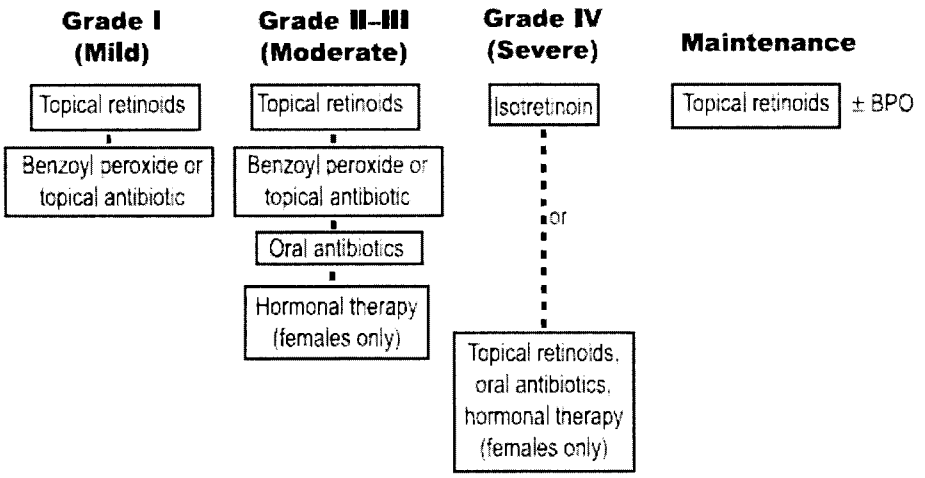
189. There is no clinical data in the '558 and '044 patents describing the efficacy and/or tolerance of 0.3% adapalene formulations in the treatment of nodulocystic acne and/or acne conglobate. (DTX 35 at GAL0022865-66)

190. In 2002, not only was it known that topical retinoids could be used to treat comedonal aspects of severe acne, but it was also known that topical retinoids were compatible and tolerable with other agents, such as benzoyl peroxide, erythromycin, and clindamycin, and could be used in conjunction with the antimicrobial agents to treat more severe types of acne. (*See* PTX 172 at 9 (indicating that topical retinoids facilitate the penetration of other acne medications)) Oral compositions, such as retinoids or antibiotics, were known to be effective in treating severe acne. (Tr. at 1014:14-1015:9)

191. It was also known by those skilled in the art that 0.1% adapalene had been used in conjunction with antibiotics to treat severe forms of acne. (*See* Tr. at 1306:10-1307:12)

192. In 2002, persons of ordinary skill in the art considered the use of topical retinoids in conjunction with antimicrobials and oral antibiotic agents as part of a well-known treatment algorithm for treating severe forms of acne. (*See, e.g.*, PTX 188 at 2; Tr. at 1309:15-21) Dr. Orlow testified the use of combination therapy "was based on 30 years of experience of tens of thousands of dermatologists around the world treating severe acne." (Tr. at 1306:10-1307:3)

193. "Most experts in the treatment of acne [in 2001] would have little quarrel with the treatment algorithm" depicted below, instructing topical retinoid use to treat severe forms of acne:



(*See* PTX 188 at 1-2; Tr. at 1145:24-1147:6; 1307:25-1308:14)

194. Currently, it is common practice for persons of ordinary skill in the art to treat severe forms of acne by prescribing 0.3% adapalene and other topical retinoids that are approved for the treatment of acne vulgaris. (*See* PTX 231 at 249 (suggesting the use of 0.3% adapalene "alone or in combination with antimicrobials depending on the severity of the disease"); PTX 250 at GAL000248236)[4] Dr. Orlow testified, "[t]reating severe acne is ***always off label***" with topical retinoids. (*See* Tr. at 1369:8-15) Even Dr. Maibach, when asked "How were the topical retinoids used to treat severe forms of acne," answered, "[a]s an adjunct or ***combination***." (Tr. at 1015:7-9 (emphasis added))

B. One of Ordinary Skill in the Art in 2002 Would Understand that the Inventors Actually Invented a 0.3% Adapalene Gel that Could Be Used to Treat Severe Acne

195. One of ordinary skill in the art would read the data presented in the patents and the description of the different types of acne in the specifications to understand that the inventors

[4] Even though the Zaenglein article (PTX 250) was published in 2006, the information in it regarding treatment algorithms reflects what would have been known by one of ordinary skill in the art in 2002. This is indicated by the consistencies with the algorithms presented in DTX 520 at S38 (published in 2003, but acknowledged by Dr. Thiboutot, a named author on the publication, to reflect knowledge in the art in 2001-2002) and PTX 188 at 2 (published in 2001). (*See* Tr. at 1390:25-1391:20; *see also* 1195:8-15)

invented compositions and methods for the treatment of acne, including acne conglobata and nodulocystic acne. (*See* Tr. at 1306:10-1307:8; 1309:15-21)

196. The specifications state: "The compositions according to the invention are particularly suitable for the treatment of acne," without distinguishing among the types of acne lesions. (*E.g.*, PTX 3 at 4:20-21)

197. One of ordinary skill in the art would have understood that, as of the priority dates of the patents-in-suit, using a 0.3% adapalene formulation for the treatment of severe forms of acne, as explicitly described in the specification, could entail the use of combination therapy, which had been used in the prior art for decades. (PTX 188 at 2; Tr. at 1305:18-1307:12; 1309:15-21)

198. Accordingly, the patents' specifications, in light of the knowledge in the art regarding acne, provide adequate written description for the use of 0.3% adapalene to treat severe acne, including nodulocystic acne and acne conglobata. (Tr. at 1306:10-1307:8; 1309:15-21)

IV. CLAIMS 2, 35, AND 36 OF THE '181 PATENT AND CLAIMS 3, 40, AND 41 OF THE '044 PATENT DO NOT INCLUDE NEW MATTER, HAVE A MARCH 12, 2002 PRIORITY DATE, AND ARE NOT ANTICIPATED BY WO 03/075908

199. The French priority application filed in March 2002 teaches that the claimed 0.3% adapalene composition may contain inactive ingredients such as "stabilizers." The specification states: "The pharmaceutical composition according to the invention can also contain inert additives or combinations of these additives, such as . . . stabilizers." (PTX 42 at GAL000097264)

200. This same language appears in the disclosures of the other priority applications. (PTX 1 at 3:9-25; DTX 164 at 5; PTX 6 at GAL000088617)

201. A person of ordinary skill in the art would understand the term "stabilizers," as used in the priority applications, to include and describe: polysaccharidic biopolymers, gums, alginates, modified celluloses, starch derived products, and a mix of polysorbate 80 and isohexadecane and acrylamide/sodium acryloyldimethyltaurate. (Tr. at 114:15-116:16; 120:5-10)

202. It was common knowledge in March 2002 that "polysaccharidic biopolymers, gums, alginates, modified celluloses, starch derived products, mix of polysorbate 80 and isohexadecane and acrylamide/sodium acryloyldimethyltaurate" and "mixtures thereof" are all thickeners or viscosity-increasing agents (i.e. "stabilizers"). (Tr. at 111:1-113:17; 172:15-175:14; 857:18-858:6)

203. It was further understood by persons of ordinary skill in the art in March 2002 that these inactive ingredient "stabilizers" inhibit the phase separation in formulations such as suspensions, gels, emulsions, and other multi-phase systems by thickening or increasing the viscosity of the formulation. (Tr. at 111:1-113:17; 172:15-175:14)

204. "[P]olysaccharidic biopolymers, gums, alginates, modified celluloses, [and] starch derived products" were commonly known and used in the art as stabilizers in March 2002. (Tr. at 111:1-113:17; 116:17-119:22; 857:18-858:6)

205. A "mix of polysorbate 80 and isohexadecane and acrylamide/sodium acryloyldimethyltaurate," such as Simulgel 600, was also commonly known and used in the art as a viscosity increasing or stabilizing agent in March 2002. (Tr. at 118:15-120:4)

206. The French priority application also supports the disclosure of "mixtures thereof." The French priority application states: "The pharmaceutical composition according to the invention can also contain inert additives or combinations of these additives . . . ." (PTX 42 at

GAL000097264) A person of ordinary skill in the art would understand "combinations of these additives" to support the disclosure of "mixtures thereof." In March 2002, a person of ordinary skill in the art would know how to combine the ingredients listed in column 3 of the '377 patent to formulate an aqueous gel medium. (Tr. at 120:10-123:2)

207. Additionally, the French priority application states that a person of ordinary skill in the art would understand how to select the various inactive ingredients in such a way that doing so would not substantially, adversely affect the advantageous properties of the invention. The specification states: "[T]hose of ordinary skill in the art will take care to select the optional compound(s) to be added to these compositions in such a way that the advantageous properties intrinsically attached to the present invention are not, or are not substantially, adversely affected by the envisaged addition." (PTX 42 at GAL000097264-65)

208. The knowledge and teaching in the art in March 2002 provided guidance on how to make and use aqueous gels containing, *e.g.*, "polysaccharidic biopolymers, gums, alginates, modified celluloses, starch derived products, mix of polysorbate 80 and isohexadecane and acrylamide/sodium acryloyldimethyltaurate, and mixtures thereof." (*E.g.*, PTX 218 at 1517-18; Tr. at 120:11-123:2; 172:15-175:14)

209. The PTO confirmed that "it is well within the purview of the skill of the artisan at the time of the invention to adjust the concentration and range of additives in a composition during the course of routine experimentation so as to obtain the desirable type of product." (PTX 6 at GAL000088575)[5]

210. Moreover, it would have been clear to a person of ordinary skill in the art reading the French priority application that, through the use of the term "stabilizers," the inventors

[5] Additionally, during prosecution, the Examiner determined that claims 1 of both the '181 and '044 patents, and the dependent claims asserted against Tolmar, were entitled to a priority date of March 12, 2002. (PTX 26 at GAL000096614; Tr. at 123:3-126:1)

envisioned and contemplated a variety of inactive ingredients, including polysaccharidic biopolymers, gums, alginates, modified celluloses, starch derived products, mix of polysorbate 80 and isohexadecane and acrylamide/sodium acryloyldimethyltaurate, to be used in the claimed 0.3% adapalene formulations. (Tr. at 113:18-116:23; 157:22-158:7; 172:15-175:14)

211. In light of the above, the priority applications' disclosures and knowledge in the art in March 2002 would have shown a person of ordinary skill in the art that the inventors were in possession of the claimed invention, including the use of the types of stabilizers listed above.

212. Because the specification of the French priority application and the other priority applications are enabling disclosures and provide sufficient written description support for claims 2, 35, and 36 of the '181 patent, and claims 3, 40, and 41 of the '044 patent, the claims are entitled to the March 12, 2002 filing date.

213. The March 12, 2002 filing date of the asserted claims precedes the September 18, 2003 publication date of the WO 03/075908 application.

V. THE '377, '181, '060, '588, AND '044 PATENTS WERE NOT INEQUITABLY PROCURED

A. Galderma's IND for Differin® 0.3% Adapalene Gel Does Not Rise to the Level of "But For" Materiality

1. Galderma's Phase I studies in healthy subjects are not predictive of what will be seen in acne patients

214. Galderma conducted several Phase I studies in 2000 using 0.3% adapalene gel that were reported in its IND for Differin® 0.3% Adapalene Gel. These include Study No. 2649 (performed on the faces of acne patients), Study No. 2644 (performed on the backs of healthy subjects under occlusion), Study No. 2645 (performed on the backs of healthy subjects under occlusion), and Study No. 2646 (performed on the backs of healthy subjects under occlusion). (DTX 607 Vol. 1.15 at GAL000004779-80; GAL000004820-21; GAL000004860-61;

GAL000004903, GAL000004923) The results of the 2649 study were reported in the patents-in-suit. (*E.g.*, PTX 1 at 4:60-5:30; Tr. at 364:23-365:12)

215. Dr. Czernielewski was responsible for the review and evaluation of the information contained within Galderma's IND, including the 2649 study. (Tr. at 594:24-595:25; 602:18-24)

216. Galderma also prepared a Clinical Investigator's Brochure for Topical Adapalene Gel, 0.3%, which was provided to each clinician prior to participating in Galderma's Phase II study for 0.3% adapalene gel. (DTX 607, Vol. 1 at GAL000005365-5446; Tr. at 427:16-22) The Clinical Investigator's Brochures are provided to clinicians on a confidential basis and contain compilations of all information known for a particular compound. (Tr. at 565:15-16; 1467:11-22)

217. In order to proceed into clinical trials, the sponsoring company must provide the FDA with all available clinical data and with positive statements of safety and potential efficacy. (Tr. at 552:22-553:15) As explained by Dr. Graeber, and unrebutted by Tolmar, these positive statements are needed for ethical reasons, as it would be unethical to proceed into human clinical studies if the sponsoring company believes a drug would be harmful or not efficacious. (Tr. at 549:17-551:7)

218. Within the protocol for the 2649 study, Galderma stated: "Preliminary studies in ***healthy Subjects*** (ref 1 and 2) show that the 0.3% concentration is likely to be only slightly more irritant than the 0.1% concentration." (DTX 607 Vol. 1.15 at GAL000004799 (emphasis added)) Similar statements were made in the protocols for the 2644, 2645, and 2646 studies. (*See* DTX 607 Vol. 1.15 at GAL000004842; GAL000004879; GAL000004957)

219. Galderma's statements made in the protocols for the 2649, 2644, 2645, and 2646 studies are not predictive for tolerability in acne patients, as those statements were based on Phase I studies conducted on the backs of healthy individuals under occlusion. (Tr. at 367:8-23)

220. The inability to extrapolate results obtained from studies conducted on the backs of healthy volunteers to results one might obtain in acne-damaged skin was confirmed by Tolmar's expert, Dr. Howard Maibach. (*See* PTX 165 at 49-50) In a paper, Dr. Maibach concluded that the "cumulative patch test described above had failed to predict adverse reactions to skin damaged by acne or shaving, or sensitive areas such as the face." (*Id.*) At trial, Dr. Maibach did not refute the conclusions he previously reached regarding the non-predictive nature of tests conducted on the backs of healthy individuals.

221. Tests on the back of healthy volunteers under occlusion do not measure all of the symptoms of the "retinoid reaction," including scaling, itching (pruritus), burning, and dryness. (Tr. at 1103:3-1104:19)

2. Galderma's Studies in Patients With Photodamaged Skin Are Not Predictive of What Will Be Seen in Acne Patients

222. In addition to conducting Phase I studies on healthy subjects, Galderma also sponsored studies evaluating 0.3% adapalene gel for the treatment of photodamaged skin. In Study No. 2506, 0.3% adapalene was used to assess safety and efficacy in treating actinic keratoses (photodamaged skin) by applying the gel to the forearm and backs of the hand of organ transplant patients undergoing immunosuppressive therapy, a very different patient population than the teenagers typically treated for acne. (*See* DTX 607 Vol. 1.1 at GAL000000046) The results of this study were published by Dr. Euvrard in the November 2000 edition of Skin & Aging. (*See* DTX 163)

223. Study No. 9305 also used a 0.3% adapalene gel formulation to assess the safety and efficacy of that concentration to treat actinic keratoses and actinic lentigo (age spots), by applying the 0.3% gel once daily for the first 4 weeks of the study and then twice daily for the remaining 8 months of the study. (*See* DTX 607 Vol. 1.1 at GAL000000046) The average age of the patients in the 9305 study was 63. (*Id.*) The results of this study were published by Dr. Goldfarb in the November 2000 edition of Skin & Aging, and were also reported in the specifications of the patents-in-suit. (*See* DTX 161; *e.g.*, PTX 1 at 1:58-62)

224. Acne-damaged skin is far different from photodamaged skin. Photodamaged skin is "lax [sagging], yellowish, mottled, wrinkled, leathery, rough skin, that is eventually studded with neoplastic growths [precancerous growths], including various premalignant and malignant neoplasms." (PTX 200 at 836) The properties of photodamaged skin are not the same properties of a patient with skin damaged by acne. (Tr. at 912:15-18) Also, protocols for measuring tolerability between acne and photodamaged skin are different. (Tr. at 1826:10-18)

225. Dr. Goldfarb has himself written: "the inflammatory response of older skin is markedly dampened and less sensitive to the retinoid reaction. Therefore, older patients can use more tretinoin cream without problems and have the potential for greater improvement of the skin." (PTX 186 at 649)

226. At trial, during cross-examination by Tolmar, Dr. Goldfarb was asked whether, based on his paper published in 2000 (DTX 161) assessing the use of 0.3% adapalene gel for the treatment of photodamaged skin, he considered 0.3% adapalene to be useful for the treatment of acne. (Tr. at 1829:9-14) Dr. Goldfarb responded, "No." (*Id.* at 1829:15)

227. Dr. Maibach also published several articles discussing the differences between the skin types of younger and older patients and their response to different chemical agents. (*See* PTX 182; PTX 211)

3. Galderma's Phase I PK Study in Acne Patients Formed the Preliminary Basis for the Invention of the Patents-in-Suit

228. Tolmar emphasizes the following statement in Galderma's Clinical Investigator's Brochure for Adapalene Gel, 0.3%: "It is concluded from this experience that the investigational 0.3% adapalene gel formulation is safe for topical application and treatment in an expanded population of patients with acne vulgaris." (DTX 607, Amend. Vol. 1 at GAL000005441)

229. This statement was made in November 2000, *after* Galderma had obtained preliminary results for PK study 2649 around August 1, 2000, which demonstrated for the first time that 0.3% adapalene might be well-tolerated in acne patients. (*Compare* DTX 607, Vol. 1.15 at GAL000004779 (showing August 1, 2000 date for preliminary results for Study 2649), *with* DTX 607, Amend. Vol. 1 at GAL000005365-66 (showing approval of Investigator's Brochure in November 2000); *see also* Tr. at 564:23-565:11)

230. The results from this study 2649 were incorporated in the patents-in-suit, as they led to the conception of the invention. (*E.g.*, PTX 1 at 5:21-30; Tr. at 553:16-554:16)

B. Galderma's Clinical Trials for Differin® 0.3% Adapalene Gel Do Not Rise to the Level of "But For" Materiality

1. Galderma's U.S. Phase II Study Is Consistent with Representations Made to the PTO

231. The U.S. Phase II study was a twelve-week, randomized, investigator-blinded, balanced parallel-group, active- and vehicle-controlled study conducted in the United States. (PTX 302 at GAL000022847.)

232. Galderma's Phase II study was designed to determine efficacy of the adapalene gel 0.3% compared to the vehicle, to assess the magnitude of treatment differences between the 0.3% and 0.1% concentrations, and to assess the systemic safety profile of 0.3% adapalene as compared to 0.1% adapalene. (PTX 219 at 146) Dr. Graeber testified that he did not know the answers to those questions prior to obtaining the results from the U.S. Phase II Study. (Tr. at 573:5-574:15)

233. The results of the U.S. Phase II study were published in Pariser et al., *The Efficacy and Safety of Adapalene Gel 0.3% in the Treatment of Acne Vulgaris: A Randomized, Multicenter, Investigator-Blinded, Controlled Comparison Study Versus Adapalene Gel 0.1% and Vehicle*, 76 Cutis 145-51 (2005) ("Pariser"). (PTX 219) One of the named inventors on the patents-in-suit, Dr. Graeber, is an author on the Pariser paper. (*Id.* at 145) The Pariser paper summarized the U.S. Phase II Study as follows:

> The results of this study show that adapalene gel 0.3% was superior to adapalene gel 0.1% and vehicle treatment of moderate to moderately severe acne while retaining a similar safety and tolerability profile to adapalene 0.1% gel.

(*Id.* at 145, Abstract) Dr. Graeber agreed with this statement when it was made and continues to agree with it today. (Tr. at 590:22-591:19)

234. Both Drs. Graeber and Dr. Czernielewski believe that the results of the U.S. Phase II Study with respect to efficacy, onset of action, and tolerability of the 0.3% adapalene gel, as compared to the 0.1% adapalene gel, are surprising. (Tr. at 416:14-417:19; 574:16-575:10; 580:2-581:25; 1804:13-1805:21; 1820:1-1821:22) The PTO, Dr. Orlow, and Dr. Thiboutot agreed. (PTX 36 at GAL000097142-43; Tr. at 1255:7-1257:4; 1471:24-1473:13)

a. Efficacy

235. There are no statements in the specifications of the patents-in-suit, or in the prosecution histories, requiring efficacy of the 0.3% adapalene gel to be statistically significantly superior to the efficacy of the 0.1% adapalene gel. (Tr. at 1525:16-24)

236. Instead, the patents only require "***better therapeutic efficacy*** compared to known compositions," and "***greater therapeutic effect*** . . . ." (*E.g.*, PTX 1 at 2:5-6; 4:58-59 (emphasis added)) Similarly, during prosecution, Ms. Baumeister stated "applicants were able to obtain, surprisingly, quicker onset and great[er] efficacy without increasing side effects when they tripled the topical dosage of adapalene from 0.1 % to 0.3%." (PTX 14 at GAL000088609 (emphasis added))

237. The U.S. Phase II Study established that 0.3% adapalene gel exhibits greater efficacy than the 0.1% adapalene gel. (PTX 219)

238. Even if statistical significance was required, the data from the Phase II Study ***did establish*** that the 0.3% adapalene gel was statistically significantly more effective when compared to the 0.1% adapalene gel. (Tr. at 1490:3-25)

239. Specifically, the U.S. Phase II Study showed that adapalene 0.3% gel was statistically significantly better than adapalene 0.1% gel, in terms of reducing the total number of lesions, reducing the number of non-inflammatory lesions, and reducing the global severity grade of the acne. (Tr. at 1490:3-1491:12)

b. Onset of Action

240. The patents state that the data from the U.S. Phase II Study "lead to the following conclusions: the 0.3% adapalene gel acts more rapidly than the 0.1% adapalene gel; specifically, from the fourth week of treatment, a ***difference*** is noted between the effectiveness of the 0.1% adapalene gel and the 0.3% adapalene gel; the 0.3% adapalene gel produces a clearly greater

therapeutic effect after eight weeks of treatment." (*E.g.*, PTX 3 at 5:27-36 (emphasis added); Figures 1, 2, and 3 of PTX 1-5) The patents do not require that the difference in onset of efficacy between the 0.1% and 0.3% gel groups be statistically significant.

241. These statements in the patent regarding the speed of onset of action correspond to the U.S. Phase II Study data.

242. Specifically, the U.S. Phase II Study Report shows that, by week 4, the improvement seen in the 0.3% group was greater than the improvement seen in the 0.1% group with respect to total lesions, inflammatory lesions, and noninflammatory lesions. (PTX 302 at GAL000022897 (Table 6), GAL000022899 (Table 8), GAL000022902 (Table 10))

243. At week 8, the improvement seen in the 0.3% group was also greater than the improvement in the 0.1% group, with respect to total lesions, inflammatory lesions, and noninflammatory lesions. At week 8, all those differences between the two groups were statistically significant. (PTX 302 at GAL000022897 (Table 6), GAL000022899 (Table 8), GAL000022902 (Table 10))

c. Tolerability

244. The patents present a table of adverse event data from the U.S. Phase II Study and state, "[f]rom this table, it is noted that the occurrence of undesirable side effects is statistically the same for the two gels with the different concentrations of active agent." (*E.g.*, PTX 1 at 6:1-3)

245. Persons of ordinary skill in the art recognize that the phrase "statistically the same," as used in the specification of the patents-in-suit, means "not statistically significantly different." This is the interpretation of every clinical dermatologist involved in this case -- and of Dr. Thisted, considering the data in the patents as a whole. (*See, e.g.*, Tr. at 1150:1-1151:4; 1407:20-24; 1493:12-1494:21)

246. Scientific papers published in peer reviewed journals prior to and after the filing date of the patents-in-suit use the phrase "statistically the same" in reference to data demonstrating no statistically significant difference. (PTX 203 at 8 (Table 3) ("Two data sets are the statistically the same if the p-value is larger than 0.05."); PTX 276 at 336-37 ("Statistical analysis of variance using repeated measures failed to indicate any differences between the IOP response of [the two groups]. . . . IOP responses were statistically the same between the two groups. . ."); Tr. at 714:8-715:12)

247. Looking at the data in the table in the patent, there are no statistically significant differences between the adapalene 0.3% gel and adapalene 0.1% gel treatment groups for any of the local undesirable side effects, either individually or in the aggregate. (Tr. at 1495:11-1496:23)

248. It would be incorrect to interpret the phrase "statistically the same" to mean identical in number, as the table in the patents-in-suit clearly reflects that both the total number of incidences of side effects associated with the 0.3% adapalene gel and some of the individual side effects, *e.g.*, dry skin, are numerically higher than the number of incidences associated with the 0.1% adapalene gel. (*E.g.*, PTX 1 at 5:42-61; Tr. at 1494:2-14)

249. As demonstrated by the Examiner's Reasons for Allowance, the Examiner considered the evidence presented to show that side effects were minimized—not that the occurrence of side effects was identical between the two formulations. The Examiner stated that "the particular dosage of 0.3% adapalene was more effective than 0.1% adapalene in treating lesions ***while minimizing side effects***." (DTX 143 at TOL172306-07 (emphasis added))

2. Galderma's U.S. Phase III Study Is Consistent with Representations Made to the PTO

a. Efficacy

250. The results of the U.S. Phase III study were published in: Thiboutot et al., *Adapalene Gel 0.3% for the Treatment of Acne Vulgaris: A Multicenter, Randomized, Double-Blind, Controlled Phase III Trial*, 54 J. Am. Acad. Dermatol. 242-50 (2006) ("the Thiboutot article"). (PTX 231) Dr. Graeber, a named inventor on the patents-in-suit, is also an author on this paper, which was written after Galderma had obtained the results to the U.S. and European Phase III Studies. (PTX 231 at GAL000240815; Tr. at 591:20-592:15) The Thiboutot article states that "[t]he results of this study confirm that the adapalene gel 0.3% retains the safety profile of the 0.1% formulation." (PTX 231 at GAL000240821) Dr. Graeber believed this statement, which is consistent with the patents-in-suit, to be true. (Tr. at 592:16-24)

251. The U.S. Phase III Study confirmed that the 0.3% gel was statistically significantly better than the 0.1% gel at reducing the total number of acne lesions, and at improving the success rate of treatment. (Tr. at 1505:8-23; 1506:20-1507:8)

252. The FDA concluded that "based on GEE analysis statistical superiority was demonstrated," and "[h]aving agreed with the sponsor on use of the GEE methodology at prior [sic], the division concurs that the [0.]3% wins over the [0.]1%." (PTX 346 at GAL000054532, GAL000054535)

b. Onset of Action

253. The U.S. Phase III Study data and results are consistent with the statement in the patents regarding speed of onset of action, *i.e.*, onset of efficacy. The patents state, "the 0.3% adapalene gel acts more rapidly than the 0.1% adapalene gel; specifically, from the fourth week of treatment, a ***difference*** is noted between the effectiveness of the 0.1% adapalene gel and the

0.3% adapalene gel," and that a clearly greater therapeutic benefit is observed by week 8. (*See, e.g.*, PTX 3 at 5:27-36 (emphasis added); Figures 1, 2, and 3 of PTX 1-5)

254. The U.S. Phase III Study does demonstrate that 0.3% adapalene reaches efficacy faster than 0.1% adapalene. For instance, the U.S. Phase III Study shows numerically greater improvements at week 4 for the 0.3% gel, compared to the 0.1% gel, in total lesion counts, noninflammatory lesion counts, and success rate (i.e., % of patients that were clear or almost clear). (Tr. at 1526:11-1527:24; 1528:16-1529:4)

c. Tolerability

255. Skilled artisans reviewing the patents-in-suit understand that the phrases "well-tolerated" and "good tolerance," as used in the patents-in-suit, refer not only to the incidence of side effects, but also the intensity or severity of those side effects. (Tr. at 509:7-510:1)

256. The U.S. Phase III Study concluded, like the patents-in-suit, that the 0.3% adapalene gel had comparable tolerability to the 0.1% adapalene gel. (Tr. at 1259:19-1260:15)

257. Tolerability for the U.S. Phase III clinical trial was assessed through the investigator's assessment of local tolerability at each visit and through reporting of adverse events by the subject. (PTX 231 at 243)

258. With respect to safety, Galderma concluded that there was "no increase in incidence of clinically relevant safety signals" in the 0.3% adapalene gel as compared to the 0.1% adapalene gel treatment groups. (PTX 307 at GAL000033835)

259. Galderma also observed that "[f]ew subjects experienced severe erythema, scaling, dryness, or stinging/burning, with comparable incidence in the Adapalene Gel, 0.3% and the Adapalene Gel, 0.1% treatment groups." (PTX 307 at GAL000033835)

260. Galderma also noted that "[m]ost of the signs and symptoms of skin irritation were mild to moderate in severity" and that "the incidence of signs and symptoms of skin

irritation consistently decreased over time, indicating that those events are transient during the first weeks of treatment." (PTX 307 at GAL000033834)

261. Galderma concluded that the "results of this study confirm that adapalene gel 0.3% retains the safety profile of the 0.1% formulation." (PTX 231 at 248)

262. When looking at the data combined from the U.S. Phase II, U.S. Phase III, and European Phase III studies, which was submitted to the FDA, of the 39 comparisons seen in Table 17, only *two* (2/39) were statistically significant (p-value < 0.5). Specifically, in the US Phase III Study, there was a statistically significantly higher rate of dry skin in the 0.3% group than in the 0.1% group. The other statistically significant difference was seen in the European Study for irritant dermatitis, which was not measured the same way in the European Study as it was in the U.S. Studies. (Tr. at 1437:12-1439:16; 1531:22-1533:14)

3. The Data from the European Phase III Study, While Consistent with the Statements in the Patents-in-Suit, Was Unreliable

263. In addition to the U.S. Phase II and III clinical trials, Galderma also conducted a clinical trial in Europe. This trial, however, was unreliable due to deficiencies in its design.

a. Efficacy

264. The European Phase III Study suggested that the 0.3% gel was better at decreasing the number of acne lesions than the 0.1% gel. (Tr. at 1524:19-1525:15)

265. The differences in efficacy between the 0.1% and 0.3% groups in the European Phase III Study did not reach statistical significance. (PTX 313 at GAL000037796)

266. Neither the specification of the patents-in-suit, nor their prosecution histories, contain any statements requiring 0.3% demonstrate statistically significantly more efficacy when compared to 0.1% adapalene gel.

267. Accordingly, the fact that the European Phase III Study did not reach statistical significance is not inconsistent with any representations made to the PTO. (Tr. at 1525:25-1526:5)

268. The lack of statistical significance was likely due to flaws in the design and execution of the European Phase III Study, including it lacking a vehicle arm. (Tr. at 1516:11-1517:1; 1523:2-7)

269. The FDA has provided guidance specifically regarding acne clinical trials indicating that "[a] demonstration of superiority against a placebo arm is generally needed for clinical studies." (PTX 264 at GAL000242680) Another article states that "[w]ithout a placebo group to ensure validity, the finding that there is no difference between the investigational and standard treatments can be misleading or uninterpretable." (DTX 247)

270. Unlike the U.S. Phase II and Phase III Studies, the European Phase III Study did not conduct two separate visits for "screening" and for "baseline evaluation." Separating screening from baseline (*i.e.*, two evaluations averaged) serves to minimize the effects of a statistical phenomenon known as "regression to the mean." By incorporating an interval from determination of eligibility (screening) to the initiation of treatment (baseline), it is possible to allow some of this natural reversion in symptoms to abate prior to treatment. (Tr. at 1520:20-1521:19)

271. The subjects in the European Phase III Study had an unusually high number of "major protocol violations," such as taking medications during the trial that were forbidden by the protocol, or failing to administer the treatment as required. (Tr. at 1521:20-1522:3)

272. The European Study results were only analyzed using the LOCF ("Last Observation Carried Forward") method. (Tr. at 1522:4-1523:1)

273. The FDA Guidance states that "LOCF might not be the optimal approach for handling dropouts; however, it is frequently applied because of simplicity." (PTX 264 at GAL000242688)

b. Onset of Action

274. The improvements in total lesion counts in the European Phase III Study show greater improvement for the 0.3% adapalene gel than the 0.1% adapalene gel starting in week 2, the first time efficacy was measured in the study. (DTX 24 at GAL000037896-901, GAL000037862-64)

275. At each time point, including those beginning in week 4, the 0.3% formulation shows greater improvement faster than the 0.1% formulation, *e.g.*, for any given level of improvement, the 0.3% patients arrived at that point earlier. (Tr. at 1529:5-23) These results are consistent with statements made in the patents regarding onset of action. (Tr. at 1529:5-23)

c. Tolerability

276. The European Phase III Study concluded that adapalene gel 0.3% had a good safety profile in the treatment of acne vulgaris. (PTX 313 at GAL000037810) This is consistent with statements made to the PTO in the specification and during prosecution that the 0.3% adapalene gel exhibits "good tolerance" when compared to the 0.1% adapalene gel. (*E.g.*, PTX 3 at 2:24-29)

277. The FDA stated:

> [T]he EU study (RD.03.SRE.2673) compared the proposed 0.3% formulation to a European gel, 0.1%, formulation and ***did not include a vehicle arm***. It differed from the US study in several important ways: it used different inclusion criteria; it assessed efficacy on the basis of lesion counts, and for the Investigatory Global Assessment it used a 12 grade scale that ***markedly differed from that used in the US Phase 3 trial. It was not designed to assess topical safety in the same way as the US trial***.

(DTX 233 at TOL165490 (emphasis added))

278. Further, "[n]o comparisons were made to the pivotal study (U.S. Phase III Study) due to the ***substantial differences in study design***: lack of a vehicle arm, different inclusion criteria and different Endpoint analyses." (*Id.* at TOL165522 (emphasis added))

C. Dr. Graeber Did Not Act With an Intent to Deceive

279. Tolmar cross-examined Dr. Graeber for a day and a half. Dr. Graeber repeatedly, and credibly, testified that statements made by Galderma in the IND, and the statements and results obtained from the U.S. Phase II, U.S. Phase III, and European Phase III Studies, were consistent with the results and statements reported in the patents-in-suit. (*E.g.*, Tr. at 416:14-417:19; 468:23-470:3; 472:11-473:10; 520:6-14; 573:11-583:8; 590:22-592:24; 598:7-15)

280. Dr. Graeber's testimony was corroborated by contemporaneous internal documents and peer reviewed publications confirming his and Galderma's belief that the U.S. Phase II, U.S. Phase III, and European Phase III Studies demonstrated that 0.3% adapalene was more efficacious, but had a comparable tolerability profile when compared to the 0.1% adapalene composition, and also reached efficacy faster than the 0.1% composition. (*See, e.g.*, DTX 29 at GAL000109967-68; PTX 219; PTX 231)

281. Dr. Graeber did not withhold any information from the PTO with an intent to deceive or make any false statements. A more plausible inference is that Dr. Graeber believed certain data was entirely consistent with the representations made to the PTO, and thus there was no requirement to submit them to the PTO.

282. Moreover, statements in the patents regarding the "surprising" and unexpected results obtained from the clinical trials are not false. Dr. Graeber, looking at his own work, can express the opinion, ***from his own perspective***, that the 0.3% adapalene concentration may be

effective and tolerable for use with acne patients, but at the same time state that the result would be unexpected to a person of ordinary skill in the art.

283. Similarly, the statements in the patents concerning the onset of action are not false. A reasonable inference is that Dr. Graeber did not believe the patents referred to any statistical superiority when it came to onset of action.

284. With respect to the phrase "statistically the same" in the specifications of the patents-in-suit, Dr. Graeber testified that looking at the phrase and the particular reference to the table in the patents-in-suit, that phrase conveys the notion that there are no meaningful, material differences between the values reported in the table. (Tr. at 614:13-615:11) The data in the table from the Phase II trial, and in the Phase III trials, are consistent with Dr. Graeber's interpretation of the phrase "statistically the same," as there are no meaningful clinical differences in the incidence of side effects between the two concentrations of adapalene. (*E.g.*, PTX 1 at 5:42-61; Tr. at 1494:2-14)

285. Further evidence of Dr. Graeber's good faith is the fact that he published the results and conclusions from the U.S. Phase II and Phase III Study reports. (*See* PTX 219; PTX 231)

D. Dr. Czernielewski Did Not Act With an Intent to Deceive

286. Although Tolmar contends that Dr. Czernielewski knew that the U.S. Phase II and U.S. and European Phase III Clinical Studies contradicted statements made to the PTO, the evidence does not support this contention.

287. Dr. Czernielewski testified that the results of those clinical trials were entirely consistent with the data presented to the PTO, and any differences in the European Phase III Study were due to the lack of a vehicle arm. (Tr. at 1803:13-1804:2; 1809:7-1811:5; 1812:23-1813:5 ("[T]he -- results of the Phase II and Phase III are quite -- U.S. studies are quite

consistent and results are comparable. The Phase III studies in Europe have this inconsistency in the design, not having the vehicle arm, but once more, from the safety point of view, tolerance point of view, to -- tolerance could be compared or could be judged comparable with the U.S. studies."); 1812:11-1818:16) Intent to deceive is not the single most reasonable inference to be drawn from the evidence.

288. With respect to the internal FDA documents (DTX 233), there is no evidence that Dr. Czernielewski received these documents or was even aware of their existence. Dr. Czernielewski could not have intentionally withheld documents of which he was not aware.

289. Finally, the submission of Galderma's Clinical Trial Study Reports to the FDA does not warrant an inference of intent to deceive the PTO. Dr. Czernielewski testified that the FDA required submission of all clinical trial studies. (Tr. at 1798:1-5 ("It is an FDA requirement to submit all the clinical experience with the product in the IND submission. That's why Galderma compiled all the studies which were performed with adapalene 0.3[%] and submitted it to the FDA.")) Under all the circumstances, a reasonable inference is that Dr. Czernielewski intended for Galderma to comply with FDA regulations, not to deceive the PTO.

VI. INVENTORSHIP UNDER 35 U.S.C. § 102(f)

290. The patents-in-suit include both composition claims and claims directed to methods of treating acne using pharmaceutical compositions.

291. Drs. Graeber and Czernielewski are the named joint inventors of the patents-in-suit and have been regarded as such throughout prosecution. (PTX 6, *e.g.* at GAL00088498-515; PTX 19)

292. Dr. Czernielewski oversaw the 0.3% adapalene project during his time at Galderma R&D in Princeton, including "development of 0.3 percent adapalene[,] . . . participat[ion] in the preparation of this clinical program, participat[ion] in the meeting with

FDA to prepare this program, and agree[ing] with this program to [the] FDA." (Tr. at 1786:1-17; 1783:14-20) He was consulted for reviewing the 0.3% protocols and followed the Phase II clinical study "closely," reviewing the results once when they came out. (Tr. at 1784:16-21; 1786:22-1787:2; 1728:4-1730:7)

293. Dr. Czernielewski, upon reviewing "the results of the Phase II study, was part of the idea to put this unexpected result into the . . . patent." (Tr. at 1802:23-1803:12)

294. When Dr. Czernielewski left the Princeton facility, Dr. Graeber took over the responsibility for the 0.3% adapalene clinical development work. (Tr. at 1785:12-25) Dr. Graeber supervised the implementation and completion of the Phase II study, and the analysis and interpretation of the data. (Tr. at 296:20-297:15) He developed the 0.3% adapalene product from Phase II to final submission and was involved in the approval process by preparing briefing packages and attending meetings with the FDA. (Tr. at 301:22-302:2; 303:5-10; 306:11-15; 348:23-349:1.) Dr. Graeber approved the final Phase II clinical study report, which is the study that provides the data included in the patents. (Tr. at 297:8-15) Dr. Graeber was also involved in the clinical interpretation of the data submitted in the patents. (Tr. at 312:11-313:20)

295. It was only when the results of the Phase II study were analyzed and understood that the conception of the claimed invention was completed. Both Drs. Czernielewski and Graeber contributed to that conception.

296. The excipients used in the 0.3% gel formulation, and their combination, were well known in the prior art. The prior art, for instance, lists a gel consisting of propylene glycol, carbomer 940, poloxamer 182, disodium edetate, methyl paraben, sodium hydroxide, and purified water. Even Tolmar's pharmaceutical formulations expert, Dr. Potts, testified that this excipient package was not inventive. (Tr. at 727:17-728:11)

VII. STANDING

297. Galderma Research and Development, S.N.C. ("Galderma R&D"), is the assignee and owner of the patents-in-suit. The asserted patents on their face assign their rights to Galderma R&D. (PTX 1-5) Additionally, the PTO assignment records indicate that the named inventors, Drs. Graeber and Czernielewski, assigned their rights to the patents to Galderma R&D. (PTX 19; PTX 32)

298. The other plaintiffs in this matter are Galderma S.A. and Galderma Laboratories, L.P. ("Galderma Labs").

A. The 1995 License Between CIRD Galderma (Galderma R&D) and Galderma S.A.

299. CIRD Galderma (the entity that eventually became Galderma R&D) and Galderma S.A. entered into a license agreement on June 1, 1995 ("1995 agreement"). (PTX 56 at GAL000088237) The 1995 agreement provided Galderma S.A. "a right, license and authority to ***use*** CIRD's ***patents*** and ***Know-how*** to ***make, have made, and sell*** the PRODUCTS listed in Schedule 'A' in the Territory." (PTX 56 at GAL000088238 (emphasis added))

300. Schedule A of the license includes the product "Adapalene Gel (known under Galderma's trademark <<DIFFERIN>>)." (*Id.* at GAL000088244)

301. "Know-how" is defined as: "knowledge, skills, Know-how, methods, inventions, trade secrets, ***patents***, models, proprietary information, technical information, and data relating to the PRODUCTS." (*Id.* at GAL000088237 (emphasis added)) Accordingly, the license covers patents relating to Differin® Gel.

B. 2004 Exclusive License Between Galderma R&D and Galderma S.A.

302. An exclusive license agreement between Galderma R&D and Galderma S.A. was signed on December 23, 2004 ("2004 agreement"). (*See* PTX 57 at GAL000088249; PTX 59)

303. The 2004 agreement recognizes that Galderma S.A. had "commercial rights to ***the patented pharmaceutical product 'Differine'*** by virtue of the license agreement of June 1, 1995, reached with Galderma R&D" (described above), and had "logistical means and necessary competences that mean it will be able to handle this flow better." (*Id.* (emphasis added))

304. The 2004 agreement conveys to "Galderma SA an ***exclusive license for North America*** (United States) to the set of ***know-how***, processes, methods, formulas, recipes, and manufacturing secrets, ***patented*** or not, current or future, relating to the manufacture of the active ingredient Adapalene and belonging to Galderma R&D (hereinafter the 'Technology') to manufacture Adapalene or have it manufactured." (*Id.* at 1-2 (emphasis added)) The 2004 agreement then states: "Galderma R&D ***likewise*** grants to Galderma SA an exclusive right to sell the active substance Adapalene for the North American market (United States)." (*Id.* (emphasis added))

C. 1998 Exclusive License Between Galderma S.A. and Galderma Labs

305. Galderma S.A. and Galderma Laboratories, Inc. (which transferred its entire operations to Galderma Laboratories, L.P.) entered into a license agreement, effective January 1, 1998 ("the 1998 agreement"), that purports to grant Galderma Labs "the ***exclusive right***, license and authority to use the Technology to make, have made, and sell the Products under the Trademarks in the Territory during the period of this Agreement." (*See* PTX 58 at GAL000088250, GAL000088252 (emphasis added); PTX 55) "Territory" is defined, in relevant part, to mean "the fifty United States of America."

306. "Products," as defined in the license, mean "the products set out in Schedules B, C[,] D[,] and E," where Schedule B includes products sold under the trademark, Differin®. (PTX 58 at GAL000088251, GAL000088261)

307. The 1998 agreement indicates "Products" may be amended "as the parties hereto may from time to time agree in writing." (*Id.* at GAL000088251)

308. On June 19, 2007, the 1998 agreement was amended to include Differin® Gel, 0.3% in the list of licensed "Products" in Schedule B. (PTX 55)

309. The June 29, 2007 Amendment is entitled, "Amendment Four to License Agreement," and expressly states that the agreement "is an amendment . . . to the Agreement made by and between **GALDERMA S.A.** ("Galderma") and **GALDERMA LABORATORIES, L.P.** f/k/a Galderma Laboratories, Inc. ("GLLP") dated January 1, 1998 ("Agreement")." (PTX 55)

VIII. INFRINGEMENT BY TOLMAR'S ADAPALENE 0.3% GEL ANDA PRODUCT

A. Tolmar's ANDA

310. Tolmar submitted ANDA No. 200-298 to the FDA seeking approval to market its proposed 0.3% by weight adapalene aqueous gel pharmaceutical composition ("Tolmar's proposed product") for the topical treatment of *acne vulgaris* (also known as common acne) in patients 12 years and older. (PTX 379 excerpt at TOL0000055)

311. The basis for Tolmar's ANDA is the reference listed drug (RLD), Differin® (adapalene) Gel, 0.3%. Differin® is the subject of an NDA held by Galderma Laboratories, L.P., for the topical treatment of acne vulgaris. (PTX 379 excerpt at TOL000055)

312. Tolmar has received tentative approval of its ANDA No. 200-298 from the FDA. (Tr. at 1976:20-22)

B. The Composition of Tolmar's Adapalene 0.3% Gel ANDA Product

313. One gram of Tolmar's proposed product will contain 3 mg adapalene, 11 mg of Carbopol® 980 (Carbomer 940), 1 mg of disodium edetate (aka edetate disodium), 2 mg of

methyl paraben, 2 mg of poloxamer 182, 40 mg of propylene glycol, sodium hydroxide, and purified water q.s. 1 g. (PTX 392 at TOL0000194; PTX 390 at TOL0000307; Tr. at 88:14-89:2)

314. The formulation of Tolmar's proposed product is as follows:

Drug Product Composition

Component	Function	IIG [a] Max	% w/w
Adapalene	Active	NA	0.3
Poloxamer 182	Wetting Agent	0.20%	0.2
Edetate Disodium, USP	Chelating Agent	0.17%	0.1
Methylparaben, NF	Preservative	0.30%	0.2
Propylene Glycol, USP	Emollient	98.09%	4.0
Carbopol 980, NF [b]	Gelling Agent	3.50% [c]	1.1
Sodium Hydroxide, NF	pH Adjustment	10.00%	qs to pH [d]
Diluted Hydrochloric Acid, NF	pH Adjustment	5.55 [e]	0.5
Purified Water, USP	Solvent	NA	qs to 100% [f]

[a] Inactive Ingredients Guidelines (FDA CDER)
[b] Carbomer Homopolymer Type C, NF
[c] IIG levels as Carbomer 940 (in a topical gel) - The RLD contains Carbomer 940. TOLMAR substituted the Carbomer 940 with Carbopol 980, an identical polymer manufactured via a benzene-free process.
[d] Approximate concentration is 0.25%, varied as necessary to attain target pH
[e] Maximum use level in a topical solution - actual concentration in a topical gel not listed
[f] Approximate concentration is 93.35%.

(DTX 613; *see* PTX 392 at TOL0000194)

315. Tolmar's product is an aqueous gel suitable for topical administration to humans. (PTX 390 at TOL0000305)

C. Tolmar's Stipulations of Infringement

316. Tolmar has stipulated to infringement of claim 35 and claim 36 of the '181 patent, claim 40 and claim 41 of the '044 patent, claim 5 of the '558 patent, and claim 24 of the '060 patent. (Tr. at 53:14-17)

D. Infringement of Claim 27 of the '060 Patent

317. Galderma has stipulated to no literal infringement of claim 27 of the '060 patent by virtue of Tolmar's use of poloxamer 182 instead of poloxamer 124 in its proposed product. (Tr. at 82:12-16)

1. Poloxamer 182 in Tolmar's Proposed Product Is Equivalent to Poloxamer 124 in Claim 27 of the '060 Patent

318. Tolmar's ANDA states: "The primary design goal was to match the innovator product as closely as possible, qualitatively and quantitatively . . . ." (PTX 392 at TOL0000196; PTX 390 at TOL0000307) Tolmar further reported to the FDA: "The TOLMAR, Inc. (TOLMAR) formulation ***duplicates*** the RLD (reference listed drug, i.e., innovator product) qualitatively (Q_1) and to the greatest degree possible, quantitatively (Q_2)." (PTX 390 at TOL0000302 (emphasis added))

319. Poloxamers 124 and 182 are used at the same concentration in the Galderma and Tolmar formulations (0.2% w/w), respectively, and are co-formulated with the same amounts of all other ingredients, including the active ingredient adapalene (0.3% w/w), to give essentially identical formulations. (Tr. at 88:14-89:7; 105:4-13)

320. Galderma and Tolmar use poloxamers in their 0.3% adapalene formulations as wetting/dispersing agents. (PTX 390 at TOL0000309 ("Functionally, poloxamer 124 & 182 serve as a dispersing or wetting agent for the API [active pharmaceutical ingredient, adapalene].")) Both poloxamers facilitate dispersion of the adapalene into a homogenous mixture within the aqueous gel. (PTX 392 at TOL0000196 ("Poloxamer functions as a wetting agent to ensure uniform API suspension and homogenous dispersion in the finished product."))

321. Tolmar's own testing demonstrated that the dispersion characteristics of poloxamers 124 and 182 in the two 0.3% adapalene aqueous gels are equivalent and "indistinguishable." (PTX 392 at TOL0000196 ("Dispersion characteristics of the two poloxamers were indistinguishable."))

322. Tolmar experimented with formulations containing both poloxamer 124 and poloxamer 182 to confirm that Tolmar's use of poloxamer 182 would not pose any problems or

result in any functional or therapeutic differences in Tolmar's generic 0.3% adapalene product, compared to the RLD, Differin® 0.3% Gel. (PTX 392 at TOL0000196) Tolmar concluded that its generic 0.3% adapalene product (containing poloxamer 182) is bioequivalent and therapeutically equivalent to Galderma's Differin® 0.3%, Gel, with comparable side effect profiles. (PTX 392 at TOL0000195 ("The substitution of poloxamer 182 for poloxamer 124 did not affect therapeutic equivalence as evidenced in the results of the bioequivalence trials . . . .""))

323. Galderma's formulations expert, Dr. Walters, explained that poloxamers are synthetic polymers that are made of "blocks" of two types of molecules or monomers: propylene oxide and ethylene oxide. Many propylene oxide molecules (C_3H_6O) form a center/core polyoxypropylene (POP) "block." That POP block is flanked on either side by many ethylene oxide molecules (C_2H_4O), which form polyoxyethylene (POE) "blocks" on either side of the center POP block. This gives poloxamers a "block copolymer" structure of: POE—POP—POE. Each block is made of varying numbers of monomer molecules. Poloxamers can vary in the approximate number of molecules comprising the POE and POP blocks. (Tr. at 89:8-20; 102:12-18; 103:4-104:3)

324. When these poloxamers are added to a suspension of adapalene in an aqueous medium, the center POP chain of both poloxamers (124 and 182) will be attracted to the surface of the adapalene particles, which are hydrophobic. This leaves the POE chains projecting into the surrounding aqueous medium. (Tr. at 90:21-92:23)

325. The projecting POE chains hinder the attraction and agglomeration (clumping) of the adapalene particles through steric hindrance. This steric hindrance results in the poloxamer acting as a dispersing agent in both Tolmar's proposed product and in the formulation described in claim 27 of the '060 patent. (Tr. at 90:21-91:24; PTX 390 at TOL0000309 ("Functionally,

poloxamer 124 & 182 serve as a dispersing or wetting agent for the API"); PTX 392 at TOL0000196 ("Poloxamer . . . ensure[s] uniform API [adapalene] suspension and homogenous dispersion in the finished product.")) The result is homogeneous, evenly dispersed adapalene particles throughout the 0.3% adapalene aqueous gel, regardless of whether poloxamer 182 or 124 is used. Tolmar concluded from its own testing that the "[d]ispersion characteristics of the two poloxamers were indistinguishable." (PTX 392 at TOL0000196; 219:12-24) Tolmar's expert, Dr. Potts, and its in-house formulator, Mr. Ebmeier, did not attempt to rebut this evidence.

326. Tolmar contends that the number of POE units between poloxamer 124 and poloxamer 182 are substantially different. (Tr. at 134:2-10) However, the ranges of values for the number of POE units in poloxamer 124 and poloxamer 182 are very similar and even overlap. (Tr. at 103:12-104:3) Further, the molecular weight ranges for poloxamer 124 and 182 also overlap. (Tr. at 102:19-20) Any small differences between the average lengths of the projecting POE chains of the poloxamers or molecular weight ranges for poloxamer 124 and 182 are insubstantial in the context of the claimed invention. (Tr. at 94:21-95:17; 103:12-104:3)

327. Tolmar also noted differences between poloxamer 124 and 182 with respect to values for Hydrophilic/Lipophilic Balance ("HLB"), cloud point, the Draves sink test, and critical micelle concentration ("CMC"). Any such differences do not impact the physical properties of the final 0.3% adapalene product. (Tr. at 97:4-102:11; 180:7-16)

328. Any differences between poloxamer 124 in the claimed invention and poloxamer 182 in Tolmar's proposed product are insubstantial.

2. Prosecution History Estoppel Does Not Apply to Claim 27 of the '060 Patent

329. As originally presented, application claims 29 and 30 from the application that led to the '377 patent are as follows:

> 29. (New) A method for treating a dermatological disorder having an inflammatory or proliferative component selected from the group consisting of common acne, comedones, polymorphous acne, nodulocystic acne, acne conglobata, secondary acne, widespread or severe psoriasis, ichtyoses, an ichtyosiform state, Darier's disease, palmo plantar keratoderma, keratosis plans and post-inflammatory pigmentation and afflicting the skin of an individual in need of such treatment, comprising administering to said individual a thus effective amount of a pharmaceutical composition which comprises on the order of 0.3% by weight of 6-[3-(1 adamantyl) 4 methoxyphonyl] 2 naphthanoic acid (adapalene) or salt thereof, formulated into a pharmaceutically acceptable medium therefor, said composition being a gel or a cream.
>
> 30. (New) The method according to Claim 29, wherein said individual is afflicted with common acne.

(PTX 6 at GAL000088521)

330. During prosecution of the '377 application, an exemplary formulation with specific amounts was added in a single amendment to application claims 29 and 30. The formulation added to each of these claims is as follows:

Adapalene	3 mg
Carbomer 940	11 mg
Disodium edetate	1 mg
Methyl paraben	2 mg
Poloxamer 124	2 mg
Propylene glycol	40 mg
Sodium hydroxide	amount required to obtain a pH of 5.0± 0.3
and	
Purified water	q.s. 1 g

(PTX 6 at GAL000088707-08)

331. The list of ingredients was originally presented in application claim 38, a claim which had been rejected earlier as obvious over, among other things, the Differin® Gel Data Sheet, which recites poloxamer 182. (PTX 6 at GAL000088523, GAL000088580; Tr. at 256:7-19)

332. Application claim nos. 29 and 30 eventually issued as claims 1 and 2 of the '377 patent. (PTX 6 at GAL000088723)

333. In allowing the claims of the '377 patent, the Examiner concluded:

> Since the present claims require the effective use of 0.3% of adapalene, and applicant has shown through unexpected results that the particular dosage of adapalene was more effective than 0.1% adapalene in treating lesions while minimizing side effects, and Shroot in view of Differin Gel Data Sheet does not render obvious ***the use of 0.3% adapalene*** as disclosed in [application] claims 29-30, claims 29-30 and 33 are therefore allowable.

(PTX 6 at GAL000088724-25 (emphasis added))

334. In Galderma's Comments on the Examiner's Statement of Reasons for Allowance, Galderma provided clear notice that "[b]roader aspects of the invention are being pursued in one or more continuing applications." (PTX 6 at GAL000088747)

335. One of those continuation applications resulted in the issuance of the '060 patent. The '060 patent, like all the patents-in-suit, was examined by the same Examiner as the '377 patent. (Tr. at 286:12-14)

336. Claims 23, 24, and 27 of the '060 patent are as follows:

> **23**. A method for treating common acne, comedones, polymorphous acne, nodulocystic acne, acne conglobata or secondary acne afflicting the skin of an individual in need of such treatment, comprising topically administering to said individual an effective amount of a pharmaceutical composition which comprises 0.3% by weight of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthanoic acid (adapalene) or salt thereof, as the sole active anti-acne agent, formulated into a pharmaceutically acceptable medium therefor, said composition being a gel or a cream.
>
> **24**. The method according to claim **23**, wherein said individual is afflicted with common acne.
>
> **27**. The method according to claim **24**, wherein the composition is a gel comprising adapalene, carbomer 940, disodium edentate, methyl paraben, poloxamer 124, propylene glycol, sodium hydroxide and purified water.

(PTX 3 at GAL000277194-95)

337. Claims 23, 24, and 27 of the '060 patent issued as filed; no amendments were made to these claims during prosecution. (*Compare* PTX 33A at GAL000096946-47 (as-filed claims 34, 35, and 38) *with* PTX 3 at GAL0000277194 (issued claims 23, 24, and 27 of '060 patent); PTX 33B; Tr. at 287:1-289:23) Unlike claims 29 and 30 of the '377 patent, they were ***never*** rejected.

338. According to the Examiner's Reasons for Allowance, the claims of the '060 patent were allowed because they "require the effective use of 0.3% of adapalene, and applicant has shown through unexpected results that the particular dosage of 0.3% adapalene was more effective than 0.1% adapalene in treating lesions while minimizing side effects. . . ." (PTX 36 at GAL000097142-43)

339. During prosecution of the '181 patent, the Examiner rejected as anticipated Galderma's pending claims that recited poloxamer 124, over the Differin® Gel Data Sheet that recited poloxamer 182. (PTX 25 at GAL000096591; PTX 26 at GAL000096620; Tr. at 260:23-

264:3) In making this rejection, the Examiner stated that poloxamer 182 listed in the Differin® Gel Data Sheet was "also known in the art as poloxamer 124." (PTX 26 at GAL000096620)

340. Subsequent to the prosecution of the '377 patent, the PTO allowed numerous claims covering 0.3% adapalene aqueous gels that did not recite poloxamer 124 specifically or even any poloxamer at all. (Tr. at 109:12-110:1; 283:21-285:21; 286:9-289:1; *see also, e.g.*, claim 35 and claim 36 of the '181 patent, claim 40 and claim 41 of the '044 patent, claim 5 of the '558 patent, and claim 24 of the '060 patent)

DISCUSSION

Trial was devoted almost entirely to Tolmar's challenges to the validity and enforceability of Galderma's patents-in-suit. Tolmar has failed to meet its burden on any of these contentions.

The discussion below begins with obviousness, as the Court discusses each of the prior art references on which Tolmar relies, explaining that none of them, singly or in combination, clearly and convincingly render Galderma's invention invalid. The Court also addresses Galderma's secondary considerations of non-obviousness. Next the Court considers each of Tolmar's additional invalidity defenses, including anticipation, improper inventorship, and lack of written description. Then the Court reviews and rejects Tolmar's allegations of inequitable conduct. After that, the Court turns to the relatively few disputes among the parties as to infringement. Finally, the Court assesses Tolmar's standing defense and explains that this case is not "exceptional" within the meaning of 35 U.S.C. § 285.

I. OBVIOUSNESS

A patent may not issue "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at

the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). Obviousness is a question of law based on underlying factual findings concerning: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). Generally, a party seeking to invalidate a patent as obvious must "demonstrate by clear and convincing evidence that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009); *see also Amgen, Inc. v. F. Hoffman–La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art."). The Supreme Court has warned, however, that, while an analysis of any teaching, suggestion, or motivation to combine known elements is useful to an obviousness analysis, the overall obviousness inquiry must be expansive and flexible. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 415, 419 (2007).

Tolmar contends that each of the asserted claims of the patents-in-suit is obvious because a skilled artisan "would have combined the Shroot patents, the Differin 0.1% Data Sheet and the Verschoore (1997) article with each other and with the Goldfarb, Euvrard, and Czernielewski references to arrive at each and every limitation of the asserted claims" of the patents-in-suit. (D.I. 317 at 10-11)[6] According to Tolmar, "[t]he only arguable difference between the subject

[6] Dr. Potts testified that the '181 and '558 patents would have been obvious to a skilled artisan in view of the asserted prior art references and combinations. Dr. Maibach testified that the same prior art would have rendered obvious the '060 and '044 patents. Both experts further opined that the '377 patent would also have been obvious in view of the asserted prior art.

matter of the Asserted Claims and the prior art . . . is the use of the specific 0.3% adapalene concentration for the treatment of acne." (D.I. 317 at 9) Tolmar argues that the asserted claims would have been obvious at the time of invention because: (1) the use of 0.3% adapalene is presumed *prima facie* obvious since it falls within the 0.01% to 1.0% concentration range previously disclosed in Galderma's own Shroot patents; and (2) a skilled artisan would have been motivated to triple the concentration of adapalene from 0.1% to 0.3% in view of the various prior art references concluding that adapalene was a well-tolerated compound with a favorable safety profile. (*Id.*)

For the reasons explained below, the Court agrees with Galderma that Tolmar has failed to establish, by clear and convincing evidence, that the claimed inventions would have been obvious to a person of ordinary skill at the time of the invention.

A. Tolmar's Obviousness Challenge Relies on a Flawed Legal Framework

As a preliminary matter, the Court agrees with Galderma that much of Tolmar's obviousness analysis substantially relies on a flawed legal framework recently rejected by the Federal Circuit. Tolmar's central argument is that because 0.3% adapalene falls within the 0.01%-1.0% range previously disclosed in Galderma's Shroot patents, the claimed inventions are *prima facie* obvious, as they involve the "mere adjustment of a concentration within a known range." (*Id.*) Tolmar further contends that because "there exists a strong *prima facie* showing of obviousness" in view of the asserted prior art, "evidence of secondary considerations simply cannot overcome the presumption" of obviousness. (*Id.*) Tolmar's reliance on the concepts of "*prima facie*" or "presumptive" obviousness, and shifting the burden to Galderma to "overcome" or "rebut" the presumption of obviousness, appear throughout Tolmar's post-trial briefing. (*See, e.g.,* D.I. 317 at 4, 9-11, 17; D.I. 331 at 1, 5)

Recently, the Federal Circuit rejected such an approach to obviousness in the context of litigation. The Federal Circuit noted that the Supreme Court "has never spoken in terms of a legally rebuttable presumption with respect to obviousness;" nor has it provided any "indication that it believes the burden of persuasion should shift to the patentee at [any] point to prove nonobviousness." *In re Cyclobenzaprine Hydrochloride Litigation*, 676 F.3d 1063, 1078 (Fed. Cir. 2012). The Court went on to state that the burden-shifting framework on which Tolmar relies – whereby a patentee must "rebut" or "overcome" a *prima facie* case of obviousness – is appropriate only in the context of patent prosecution. *See id.* at 1080 n.7 ("Courts should not apply the burden-shifting framework for . . . invalidity determinations . . . because the prosecution and litigation contexts are distinct."). The proper analysis of obviousness under 35 U.S.C. § 103 requires that "all evidence relevant to obviousness or nonobviousness be considered, and be considered collectively," without resort to presumptions of *prima facie* obviousness or burden-shifting. *Id.* at 1078.

Thus, here, the Court cannot presume that the selection of 0.3% adapalene would have been *prima facie* obvious to a skilled artisan. Instead, the Court must conduct its analysis by carefully evaluating the disclosure of the Shroot patents in light of all of the prior art identified by both parties.

B. Tolmar's Prior Art Does Not Establish a Motivation to Triple the Concentration of Adapalene from 0.1% to 0.3%

The parties' fundamental dispute on the question of obviousness concerns whether a skilled artisan would have been motivated to triple the concentration of adapalene from 0.1% to 0.3%, as of the date of invention, in view of the prior art.[7]

[7] There is no significant dispute regarding the level of ordinary skill in the art. Both sides generally agree that the hypothetical person of ordinary skill in the art would possess an advanced degree in medicine, pharmacy, or the pharmaceutical sciences, along with several

Tolmar's central argument is that the asserted claims would have been obvious because the claimed 0.3% adapalene concentrations fall within the preferred concentration ranges previously disclosed in Galderma's own earlier Shroot patents. According to Tolmar, a skilled artisan would have been motivated to increase the concentration of adapalene from 0.1% to 0.3% in view of other prior art references – including Verschoore (1997), Goldfarb (2000), Euvrard (2002), and Czernielewski (2001) – which purportedly teach or suggest that adapalene would be well-tolerated at both 0.1% and 0.3% concentrations. The Court is not persuaded by Tolmar's position, in view of the many meaningful differences between the claimed inventions and each of Tolmar's asserted prior art references.

1. The Shroot Patents

Tolmar contends that the Shroot patents render the asserted claims obvious because they "disclose various benzonaphthalene derivatives, including adapalene, and claim concentrations in the range of 0.01% to 1.0% by weight." (D.I. 317 at 8) Thus, according to Tolmar, 0.3% adapalene would have "involv[ed] the mere adjustment of a concentration within a known range." (*Id.* at 9)

The Court agrees with Galderma that the Shroot patents "disclose[] an enormous variety of different chemical compounds, different dosage forms, and different diseases that could be treated," and contain nothing that would direct a skilled artisan particularly to select 0.3% adapalene as an appropriate concentration for the treatment of acne. (D.I. 316 at 16-17, 29) Accordingly, the broad and varied scope and content of the Shroot patents – which disclose a

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years of experience in the treatment of dermatological conditions and/or the clinical evaluation of topical formulations used for such treatments. (D.I. 319 ¶ 174; D.I. 318 ¶ 353) To the extent that there are minor differences between the parties' proposed findings regarding the level of ordinary skill in the art, the Court concludes that those differences do not meaningfully impact the obviousness analysis.

large number of compositions for a variety of applications – does not, by itself, support a finding of obviousness. Indeed, when considered in view of the scope and content of the prior art as a whole, the Shroot patents weight against a finding of obviousness, as explained below. *See Genetics Institute, LLC v. Novartis Vaccines and Diagnostics, Inc.*, 655 F.3d 1291, 1306 (Fed. Cir. 2011).

2. Differin® 0.1% Gel Data Sheet

Tolmar relies on the Differin® 0.1% Gel Data Sheet to argue that the excipient package in Galderma's 0.3% adapalene formulations was in the prior art and a matter of routine and ordinary skill in the art, a point which Galderma does not dispute. (D.I. 317 at 9; D.I. 330 at 40) Hence, the parties appear to agree that the selection of the excipients recited in the asserted claims would have been a matter of routine skill and, therefore, obvious to a skilled artisan at the time of invention in view of the Differin® 0.1% Gel Data Sheet. For the reasons explained throughout this Opinion, however, even if the selection of excipients for a 0.3% gel was obvious, the selection of a concentration of 0.3% adapalene was not obvious.

3. Verschoore (1997)

Tolmar relies on Verschoore (1997) to argue that Galderma had conducted and published data from its own clinical trials indicating that 0.3% adapalene gel was well tolerated and produced a low skin irritation profile similar to 0.1% adapalene gel. However, Tolmar overlooks meaningful differences between the studies described in Verschoore (1997) and the inventions of the asserted claims.

In particular, the studies described in Verschoore (1997) were Phase I studies in which adapalene was applied to the backs and forearms of healthy patients, rather than Phase II or III studies involving the application of adapalene to the facial skin of patients afflicted with acne.

(FOF107-08) The Phase I studies described in Verschoore (1997) involved the use of "repeated insult patch test" (RIPT) and back occlusion testing rather than the application of adapalene to the facial skin of acne patients. (FOF133) Significantly, the scientific literature indicates that "[r]esults obtained via patch-testing methods that involve application to the back cannot be assumed to reliably predict facial irritation." (FOF 135) Even Tolmar's own expert, Dr. Maibach, has published a study stating that the 21-day cumulative irritation test like that used in Verschoore "had failed to predict adverse reactions to skin damaged by acne . . . or sensitive areas such as the face." (FOF 136)

The Court agrees with Galderma that the side effects, or lack thereof, that were observed in the back and forearm skin of healthy Phase I subjects described in Verschoore (1997) do not provide, to one of ordinary skill in the art, an accurate picture or reliable indication of what side effects might arise when the same adapalene concentration is applied to the facial skin of acne patients, as required by the asserted claims. Hence, one having ordinary skill in the art would not, at the time of the invention, have concluded, from Verschoore (1997) in combination with any other prior art, that treatment of acne with 0.3% adapalene was obvious.

4. Goldfarb (2000)

The Goldfarb abstract and article describe the treatment of actinic keratosis and photodamaged skin using 0.1% and 0.3% adapalene gels. The results described in Goldfarb (2000) were obtained from patients in their mid-60s. Tolmar relies on the authors' conclusion that 0.1% and 0.3% were comparable in terms of their irritation potential to argue that a skilled artisan would have understood that the same comparable tolerability profiles between 0.1% and 0.3% adapalene would also be found with acne patients.

The Court again disagrees. The evidence presented at trial establishes that there are meaningful differences between actinic keratosis and photodamaged skin, on the one hand, and acne-damaged skin, on the other hand, such that a skilled artisan would not have concluded from Goldfarb (2000) that 0.1% and 0.3% adapalene would share comparable tolerability profiles in acne patients. These are fundamentally different disorders with different etiologies generally affecting different patient populations. (FOF 150-54) Whereas acne afflicts the sensitive facial skin mostly of young or adolescent patients, patients with photodamaged skin are typically much older, and – as a result of chronic sun exposure – their skin is often thicker, drier, and less irritable. (FOF 152) Galderma presented evidence at trial that older patients with photodamaged skin can often tolerate, and may even require, higher doses of retinoids to achieve the desired effect. (FOF 153)

Tolmar's own expert, Dr. Maibach, has published multiple articles noting the reduced sensitivity and inflammatory response in the skin of elderly individuals. (FOF 154) Hence, the Court concludes that the Goldfarb (2000) studies would not have led a skilled artisan to conclude that 0.1% and 0.3% adapalene gels would share comparable tolerability profiles in acne patients.

5. Euvrard (2002)

Euvrard (2002) is unhelpful to Tolmar for reasons similar to those just discussed with respect to Goldfarb. Specifically, the Euvrard (2002) reference describes a study involving the administration of 0.1% and 0.3% adapalene to treat actinic keratoses on the hands and forearms of organ transplant patients who were likely also taking immunosuppressive drugs. (FOF 156) Euvrard (2002) has minimal value to assessing the relative tolerability profiles of 0.1% and 0.3% adapalene in acne patients, given that the facial skin typically afflicted by acne is thinner, more

sensitive, and more prone to irritation than the thicker skin found at the extremities such as the hands and forearms. (FOF 157)

6. Czernielewski (2001)

Tolmar relies on the Czernielewski (2001) reference, a review article summarizing research conducted on adapalene. Tolmar contends that a skilled artisan would have been motivated to increase the concentration of adapalene above 0.1% because Czernielewski (2001) discloses that the "primary objective in the development of adapalene was to create a topical agent with retinoid therapeutic effects that is considerably less irritating than topical tretinoin." (FOF 112) Czernielewski (2001) further summarizes various studies of adapalene which show that "adapalene is a very well tolerated compound with markedly lower irritation potential as compared with tretinoin." (*Id.*)

However, there is nothing in Czernielewski (2001) that would have motivated a skilled artisan to triple the concentration of adapalene from 0.1% to 0.3%. Notably, the studies described in Czernielewski (2001) focus primarily on the administration of 0.1% adapalene rather than higher concentrations. (FOF 114) Also, these studies indicate that 0.1% adapalene was selected as the standard or optimal concentration for the treatment of acne. (FOF 113) Thus, to the extent the Czernielewski (2001) reference would have informed a skilled artisan regarding the favorable tolerability profile of adapalene, this reference would have taught that 0.1% was the optimal concentration, which does not support a conclusion that 0.3% was obvious.

C. The Prior Art Teaches Away from Increasing the Concentration of Adapalene Above 0.1%

In addition to demonstrating meaningful differences between the claimed inventions and the prior art, Galderma also offered persuasive evidence demonstrating that the prior art taught

away from the selection of 0.3% adapalene for the treatment of acne. The Court briefly addresses these references below.[8]

1. Verschoore (1991) and Alirezai (1996)

The Verschoore (1991) article reports the results of a Phase II clinical trial conducted by Galderma in which 0.03% and 0.1% adapalene formulations, as well as 0.025% tretinoin, were applied to the faces of acne patients, in order to assess the relative efficacy and tolerability of each composition. The Court agrees with Galderma that the findings reported in Verschoore (1991) would have indicated to a skilled artisan that the 0.1% adapalene formulation resulted in clinically meaningful increases in irritation relative to the 0.03% adapalene formulation. Galderma's expert, Dr. Orlow, testified that the results reported in Table 2 of the Verschoore (1991) reference reflect notable increases in the local irritation score for a number of the measured side effects. (FOF 93)

The Alirezai (1996) article similarly reports the results of a Phase II clinical trial comparing the tolerability of 0.03% and 0.1% adapalene formulations. The Alirezai article revealed that the 0.1% adapalene formulation resulted in statistically higher scores for various

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[8] Tolmar argues that the references relied on by Galderma cannot, as a matter of law, be used to demonstrate that the prior art "taught away" from the claimed invention because those references fail to disparage or criticize the claimed invention; namely, increasing the concentration of adapalene above 0.1%. While prior art that affirmatively criticizes or disparages the claimed invention can demonstrate teaching away, such evidence is not the absolute requirement Tolmar suggests. *See Baxter Int'l, Inc. v. McGaw, Inc.*, 149 F.3d 1321, 1328 (Fed. Cir. 1998) ("[A] reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought . . . .") (internal quotation marks omitted). As will be explained, the Court concludes that the prior art cited by Galderma did, in fact, teach away from the selection of 0.3% adapalene for the treatment of acne, because it suggested a dose-dependent increase in side effects, such that tripling the concentration from 0.1% to 0.3% would have been unproductive. Additionally, the Court rejects – for the reasons set forth in Galderma's post-trial briefing (D.I. 330 at 21) – Tolmar's request that the Court disregard Galderma's evidence of teaching away in view of a recent Office Action by the Patent Office.

side effects – including severe burning after application, burning and itching after application, and persistent burning – as compared to the 0.03% formulation. (FOF 97-98)

Notably, unlike the Phase I studies relied on by Tolmar, the Verschoore (1991) and Alirezai (1996) references involved Phase II studies involving the application of adapalene formulations to the diseased skin of acne patients. (FOF 91-94, 96-98) The increased irritation observed when tripling the concentration of adapalene from 0.03% to 0.1% effectively taught away from again tripling the concentration from 0.1% to 0.3%, given the potential for further increased side effects.[9]

2. Allec (1997), Verschoore (1997), and Czernielewski (2001)

As already noted, the Verschoore (1997) and Czernielewski (2001) references both reported that 0.1% adapalene was the standard or optimal concentration for the treatment of acne. The Allec (1997) reference similarly reported that 0.1% was the optimal concentration for adapalene in the treatment of acne. These references, then, would also have taught away from tripling the concentration of adapalene from 0.1% to 0.3%, which would have been a significant deviation from the then-understood optimal concentration.[10]

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[9] Tolmar disputes Galderma's interpretation of the data reported in these references, suggesting Galderma has exaggerated the actual significance of the reported increased side effects and noting that the authors of the studies concluded that the tolerability of 0.03% and 0.1% adapalene was "equally acceptable," "similar," and/or only "slightly higher." (D.I. 331 at 14) On balance, however, the Court is persuaded by Galderma's interpretation of the results of these studies. To the extent reasonable minds can differ regarding the proper interpretation of the results, this supports the Court's overall conclusion that Tolmar has failed to meet its burden of establishing obviousness by clear and convincing evidence.

[10] These references also refute Tolmar's argument that the selection of 0.3% adapalene involved nothing more than the "routine optimization" of the concentration range previously disclosed in the Shroot patents. To the contrary, these references demonstrate that when Galderma – the world's foremost expert with respect to adapalene – attempted such optimization it arrived at 0.1% adapalene as the optimal concentration, and not 0.3%.

3. Tretinoin and Tazarotene

The Court also agrees with Galderma that the experience with other topical retinoids, such as tretinoin and tazarotene, further taught away from tripling the concentration of adapalene from 0.1% to 0.3%. Tolerability problems encountered with tretinoin and tazarotene led to ***downward*** adjustments in the concentrations of these retinoids as used for the treatment of acne. (FOF 84, 87) This created an expectation that a similar experience would be present with adapalene, thereby again teaching away from an ***upward*** adjustment from 0.1% to 0.3%.[11]

D. Secondary Considerations of Non-Obviousness

The Court further concludes that at least two secondary considerations, unexpected results and commercial success, additionally support the determination that the asserted claims are not invalid due to obviousness.

1. Unexpected Results

Galderma contends that the comparable tolerability of 0.1% and 0.3% adapalene was unexpected in view of the prior art, since a skilled artisan would have expected that tripling the concentration of adapalene would have resulted in a clinically significant increase in side effects. In response, Tolmar raises a number of legal and factual arguments as to why Galderma should not be permitted to rely on unexpected results. None of Tolmar's contentions is persuasive.[12]

First, Tolmar contends that Galderma is precluded from relying on the favorable tolerability profile of 0.3% adapalene because the Court's claim construction excludes

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[11] Galderma also relies on the Overdosage warning contained in its Differin® 0.1% Gel Data Sheet as evidence that the prior art taught away from increasing the concentration to 0.3%. The Court agrees with Tolmar that the Overdosage warning is not significant evidence of nonobviousness, as it was required by law, *see* 21 C.F.R. § 201.56, and was directed to patients rather than to a skilled artisan.

[12] While the secondary considerations described in this section support Galderma's position that the asserted claims are nonobvious, it was unnecessary for Galderma to have proven secondary considerations, given the Court's conclusions regarding obviousness.

tolerability from the scope of the asserted claims. However, as the Federal Circuit recently explained, "every property of a claimed compound need not be fully recognized as of the filing date of the patent application to be relevant to nonobviousness," as "relevant secondary considerations often are not manifest even until well after the issuance of a patent." *Genetics Institute*, 655 F.3d at 1307-08.[13] As even Tolmar's own post-trial briefing implicitly acknowledges, unexpected results can arise after the filing or issuance of a patent. (*See* D.I. 331 at 18-19) (noting "it is common practice for parties to file patent applications on new drugs before human clinical testing has commenced," and beneficial properties subsequently discovered during clinical trials can constitute unexpected results). Nothing about the Court's claim construction renders irrelevant, as a secondary consideration of non-obviousness, evidence that the tolerability profile of 0.3% adapalene is unexpected.

Second, Tolmar contends that Galderma improperly relies on other retinoids, such as tretinoin and tazarotene, to demonstrate unexpected results, while the Federal Circuit has considered unexpected results only when compared to the closest prior art. *See Kao Corp. v. Unilever United States, Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.") (internal quotation marks omitted). Here, the closest prior art is Verschoore (1991) and Alirezai (1996), both of which, for reasons already explained, disclose a dose-dependent increase in side effects when the concentration of adapalene is increased from 0.03% to 0.1%. Thus, the prior art as a whole demonstrates unexpected results, even crediting Tolmar's legal assertion and ignoring tretinoin and tazarotene.

[13] *See also In re Zenitz*, 333 F.2d 924, 927 (C.C.P.A. 1964); *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963).

Third, Tolmar suggests that the tolerability profile of 0.3% adapalene cannot establish unexpected results because that profile represents, at most, a difference in degree, rather than a difference in kind. *See Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322-23 (Fed. Cir. 2004) (noting that unexpected results requires difference in kind, not merely degree). In the Court's view, the evidence does show a difference in kind rather than just degree. Whereas the prior art suggested a dose-dependent, clinically meaningful increase in side effects would result from increasing the concentration of adapalene from 0.03% to 0.1%, the claimed inventions achieved a difference in kind by discontinuing that trend.[14]

Finally, Tolmar contends that the comparable tolerability of 0.3% adapalene relative to 0.1% adapalene was not unexpected, but rather would have been expected by one of ordinary skill in the art in view of the prior art. The Court disagrees. As explained in connection with the Verschoore (1991) and Allec (1996) references, comparable tolerability would not have been expected between 0.1% and 0.3% adapalene because the prior art created an expectation that clinically significant, dose-dependent increases in side effects would result from a tripling of adapalene concentrations.[15]

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[14] By contrast, cases finding mere differences in degree have generally involved situations in which the claimed invention was merely a continuation of a trend previously disclosed in the prior art. In *In re Huang*, 100 F.3d 135 (Fed. Cir. 1996), the claimed invention was a shock-absorbing grip with a polyurethane layer, and the invention merely increased the thickness of the polyurethane layer. The increased shock absorption was not unexpected because the prior art taught that shock absorption was correlated with the mechanical properties of polyurethane; thus, a skilled artisan would logically infer that increasing the amount of polyurethane would lead to an increase in shock absorption. *See id.* at 139. Similarly, in *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1323 (Fed. Cir. 2004), the increased ease of finding a handle element quickly was not unexpected for a three-grip plate when the prior art disclosed the same benefits resulted from two- or four- grip plates.

[15] The parties dispute whether the Court may consider statements in Galderma's IND regarding the purported expectation that 0.3% adapalene would be well tolerated. On balance, the Court agrees with Galderma that the IND statements were likely based on the inventors' own work, or otherwise were the result of work by other Galderma scientists, and, therefore, are unavailable as independent evidence of obviousness. *See* 35 U.S.C. § 103(c); *Life Techs., Inc. v.*

2. Commercial Success

The commercial success of Galderma's 0.3% adapalene product also supports a finding of nonobviousness. Despite being one of the most recent retinoids to reach the market, Differin® 0.3% quickly gained and maintained market share – even in the face of an overall declining market and decreasing promotional expenditures, and while facing competition from generic 0.1% adapalene formulations. (FOF 174-75, 182-84) Further, the Court agrees with Galderma that Tolmar (along with another ANDA filer, Actavis) seeks to enter the market precisely because Differin® 0.3% has been commercially successful. (FOF 185) Galderma adequately established that Differin® 0.3% is an embodiment of the patents-in-suit and that its commercial success is due to its patented features. (FOF 186-87)

* * *

In sum, as explained above, Tolmar has failed to prove by clear and convincing evidence that the inventions of the patents-in-suit would have been obvious to one having ordinary skill in the art at the time of the inventions. Additionally, although unnecessary, Galderma has proven that the prior art taught away from the claimed inventions and that certain secondary considerations of non-obviousness – unexpected results and commercial success – further demonstrate the inventions were not obvious. Hence, judgment will be entered for Galderma and against Tolmar with respect to obviousness.

II. ANTICIPATION

Tolmar argues that claims 2, 35, and 36 of the '181 patent and claims 3, 40, and 41 of the '044 patent are anticipated by WO 03/075908, which was published on September 18, 2003 and

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Clontech Labs., Inc., 224 F.3d 1320, 1325 (Fed. Cir. 2000). The Court further agrees with Galderma that, to the extent any IND statements were made prior to the pharmacokinetic study relied on by Galderma, they were simply statements of the hypothesis to be tested in subsequent clinical trials.

is the English version of the PCT application leading to the '377 patent. Tolmar's anticipation argument relies on an assertion that these claims contain new matter and, thus, are not entitled to the March 12, 2002 priority date of the '377 patent, rendering the WO 03/075908 application intervening anticipatory prior art.

The purported new matter is contained in the following claim language in independent claims 1 of both the '181 and '044 patents: "said aqueous gel medium comprises at least one ingredient selected from the group consisting of carbomers, polymeric emulsifying agents, ***polysaccharidic biopolymers, gums, alginates, modified celluloses, starch derived products, mix of polysorbate 80 and isohexadecane and acrylamide/sodium acryloyldimethyltaurate, and mixtures thereof***" (emphasis added). Tolmar contends that the emphasized language constitutes new matter.

Tolmar has not met its burden of proving anticipation by clear and convincing evidence. During prosecution, an issue of priority was raised; the Examiner determined that claims 1 of both the '181 and '044 patents, and their corresponding dependent claims asserted here against Tolmar, were entitled to a March 12, 2002 priority date. (FOF 209) The Court is not persuaded that the Patent Office's priority determination was erroneous, particularly in view of the evidence presented by Galderma at trial establishing that a skilled artisan would understand the term "stabilizers," as disclosed in the priority applications, to include the ingredients that Tolmar now asserts constitute new matter.

Because the Court agrees with Galderma that the '181 and '044 patents do not contain new matter, those claims are entitled to the March 12, 2002 filing date. Therefore, they cannot have been anticipated by the September 18, 2003 WO 03/075908 application.

III. INVENTORSHIP

Tolmar contends that the asserted claims are invalid for failure to name certain inventors and for incorrectly naming Dr. Graeber as an inventor. "Because the issuance of a patent creates a presumption that the named inventors are the true and only inventors, the burden of showing misjoinder or nonjoinder of inventors is a heavy one and must be proved by clear and convincing evidence." *Bd. of Educ. v. Am. BioSci., Inc.*, 333 F.3d 1330, 1337 (Fed. Cir. 2003).

A. Nonjoinder

Tolmar contends that the patents-in-suit are invalid for failure to name the inventors of the specific ingredients recited in the claimed formulations of the patents-in-suit. According to Tolmar, the patents-in-suit are invalid for misjoinder because "[b]oth named inventors testified that they played ***no*** role in developing the 0.3% adapalene formulations." (D.I. 317 at 25) (emphasis in original)

The Court disagrees. Inventorship requires a contribution that is beyond the exercise of ordinary skill in the art. Here, the record evidence establishes that the inactive ingredients in the claimed formulations was routine and obvious, and, therefore, non-inventive. Indeed, Tolmar argued in its post-trial briefing that "[t]he only arguable difference between the subject matter of the Asserted Claims and the prior art, if any, is the use of the specific 0.3% adapalene concentration for the treatment of acne," because "the excipient package was in the prior art and the choice of excipients is a matter of routine selection within the skill and knowledge of the ordinary skilled person." (D.I. 317 at 9) Accordingly, Tolmar's invalidity challenge based on nonjoinder of whomever devised the formulation is without merit.[16]

[16] Although Galderma fails to address the issue in its briefing, the Court concludes that none of the authorities cited by Tolmar (*see* D.I. 317 at 26) supports a finding, by clear and convincing evidence, that the patents are invalid due to the complete lack of evidence as to who initially decided to investigate the use of 0.3% adapalene to treat acne. (*See generally* Tr. at

B. Misjoinder

Tolmar also contends that the patents-in-suit are invalid for misjoinder, by improperly naming Dr. Graeber as an inventor. According to Tolmar, Dr. Graeber merely evaluated the Phase II clinical trial data. In Tolmar's view, conducting and interpreting a clinical trial is not sufficient to qualify one as a joint inventor, as such work relates to reduction to practice rather than conception. (D.I. 317)

Conception requires a definite and permanent idea of the operative invention and "necessarily turns on the inventor's ability to describe his invention." *Burroughs Wellcome*, 40 F.3d at 1228. By contrast, "[p]roof that the invention works to a scientific certainty is reduction to practice." *Univ. of Pittsburgh Commonwealth System of Higher Educ. v. Hedrick*, 573 F.3d 1290, 1299 (Fed. Cir. 2009).

Dr. Graeber supervised the implementation and completion of the Phase II study, as well as the analysis and interpretation of clinical data as reported in the patents, and also was involved throughout Galderma's regulatory submissions to the FDA. (FOF 294-95) Dr. Graeber's role in conducting and interpreting the Phase II clinical trial results was critical to the inventors' ability to meaningfully describe their invention. Otherwise, the patents-in-suit would have provided nothing more than "a mere wish or plan" to obtain the claimed invention and, thus, would have failed to adequately describe the claimed invention. *See Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2011); *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367 n.13 ("[C]onception is a prerequisite to an adequate written description."). Thus Tolmar has failed to prove, by clear and convincing evidence, that the patents-in-suit are invalid due to naming Dr. Graeber as an inventor.

61:1-4 (Tolmar's counsel observing Tolmar asked for lab notebooks and Galderma could not find any)) By contrast, in each of the cases cited by Tolmar, there was clear and convincing evidence that affirmatively identified the true inventor(s).

IV. WRITTEN DESCRIPTION

The written description "must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). The test is whether the disclosure "conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* This requires an "objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id.* Given this perspective, in some instances a patentee may satisfy the written description requirement by, in part, relying on information that is "well-known in the art." *See Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011).

The level of detail required to satisfy the written description requirement depends, in large part, on the nature of the claims and the complexity of the technology. The written description requirement "does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement." *Ariad*, 598 F.3d at 1352. However, a "mere wish or plan" to obtain the claimed invention is not sufficient. *Centocor*, 636 F.3d at 1348.

Tolmar contends that the asserted claims of the '558 and '044 patents are invalid under 35 U.S.C. § 112 for lack of written description. According to Tolmar, these patents fail to provide adequate written support for the treatment of severe forms of acne. Specifically, Tolmar argues, "[t]here is no data disclosed in the '558 and '044 patents that demonstrate 0.3% adapalene would be effective in treating severe forms of acne." (D.I. 317 at 30-31) Thus, Tolmar continues, "[t]here is no description within the four corners of the specification of the use of the 0.3% concentration to effectively treat severe acne." (*Id.*)

Tolmar has failed to establish, by clear and convincing evidence, that the inventors were not in possession of the claimed invention and its use in the treatment of severe acne. At trial, Galderma presented persuasive evidence that it was well-known in the art that topical retinoids could be used in combination with other agents as part of a treatment algorithm to treat severe acne. (FOF 192-94) While Tolmar argues "there is no suggestion or disclosure in the '558 and '044 patents of combining 0.3% adapalene with any other drug for the treatment of [severe] acne," it is equally true that the claims do not impose any requirement that the claimed compositions be used in isolation. The claims merely require that 0.3% adapalene be the only anti-acne effective agent in the topically applicable pharmaceutical compositions recited in the claims. Nothing bars the use of the claimed pharmaceutical compositions in conjunction with other anti-acne effective agents, such as oral antibiotics, in the treatment of severe acne, including as part of a treatment regimen that would have been known to one of ordinary skill in the art at the time of the invention. (FOF 192-94)

V. INEQUITABLE CONDUCT

To prevail on an inequitable conduct claim, a defendant must establish both the materiality of the withheld reference and the applicant's intent to deceive the PTO. *See Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1290 (Fed. Cir. 2011) (*en banc*). In *Therasense*, the Federal Circuit rejected the "sliding scale" approach to proving inequitable conduct, "where a weak showing of intent may be found sufficient based on a strong showing of materiality, and vice versa." *Id.* Instead, "[i]ntent and materiality are separate requirements." *Id.*

With respect to materiality, the standard is but-for materiality unless there is affirmative egregious misconduct. *See id.* at 1292. A prior art reference "is but-for material if the PTO

would not have allowed a claim had it been aware of the undisclosed prior art." *Id.* at 1291. In the inequitable conduct context, but-for materiality must be shown by a preponderance of the evidence, "giv[ing] claims their broadest reasonable construction." *Id.* at 1291–92.

To satisfy the intent requirement, "the accused infringer must prove by clear and convincing evidence that the applicant knew of the reference, knew that it was material, and made a deliberate decision to withhold it." *Id.* at 1292. Thus, inequitable conduct requires clear and convincing evidence of a specific intent to deceive the PTO. *See id.* In fact, "the specific intent to deceive must be 'the single most reasonable inference able to be drawn from the evidence.'" *Id.* (quoting *Star Scientific*, 537 F.3d at 1366).

Tolmar's post-trial briefing identifies four grounds for a finding of inequitable conduct: (1) the inventors allegedly withheld certain prior art references from the PTO during prosecution; (2) statements in Galderma's IND submitted to the FDA allegedly contradict statements made to the PTO regarding the surprising and unexpected tolerability of 0.3% adapalene as compared to 0.1% adapalene; (3) the statements regarding the more "rapid onset" of acne relief experienced with 0.3% adapalene are allegedly false and material misrepresentations; and (4) the statements in the patents employing the "statistically the same" language relating to the tolerability of 0.3% and 0.1% adapalene are allegedly false and material misrepresentations. As explained below, the Court concludes that none of Tolmar's theories of inequitable conduct are persuasive, as Tolmar has failed to demonstrate materiality and/or deceptive intent.[17]

[17] Galderma contends that the first two of the asserted grounds for inequitable conduct – the withheld prior art references and the statements in Galderma's IND – should be stricken, as they were not properly and timely disclosed by Tolmar prior to trial. The Court is inclined to agree with Galderma. However, because the Court has found that Tolmar has failed to meet its burden on any of its theories of inequitable conduct, it is unnecessary to determine whether any of Tolmar's bases for asserting inequitable conduct should be stricken.

A. Allegedly Withheld Prior Art

Tolmar contends that Galderma committed inequitable conduct by deliberately withholding three prior art references relevant to patentability: Verschoore (1993),[18] Verschoore (1997), and Euvrard (2002). Tolmar argues that these withheld references contradict the statements the applicants made to the Patent Office regarding unexpected results, because these references disclose that adapalene was known to be well-tolerated; hence, these references would have motivated a skilled artisan to test adapalene concentrations greater than 0.1%. (D.I. 317 at 39-40)

Tolmar has failed to prove that these references are but-for material. Instead, the Court agrees with Galderma that the allegedly withheld references are cumulative of prior art that was already before the Patent Office during prosecution. (D.I. 330 at 32-35) These three references are not but-for material also because of the significant differences between them and the claimed invention, as explained above in connection with the obviousness analysis.[19]

B. Statements in Galderma's IND

Tolmar contends that "both named inventors made material misrepresentations to the Patent Office concerning 'unexpected results' of good tolerability . . . obtained with 0.3%

Although not expressly discussed below with respect to each ground asserted for inequitable conduct, the Court finds no evidence of deceptive intent, as is clear from the findings of fact. (FOF 279-89)

[18] Verschoore (1993) is an article entitled, *Topical Retinoids*, 11 Dermatol. Clinics 107-15 (1993). (PTX 280) It is a summary article that cites to data appearing in other articles. The portions of Verschoore (1993) relied upon by Tolmar refer to data from Verschoore (1991), which demonstrated a trend of increased irritation when increasing the concentration of adapalene from 0.03% to 0.1%. Although Tolmar asserts Verschoore (1993) in connection with its inequitable conduct allegations, it does not assert Verschoore (1993) as part of any prior art combination that it contends would have rendered the claimed inventions obvious at the time of invention. (D.I. 317 at 11)

[19] The differences between the allegedly withheld references and the claimed inventions are so substantial that an Examiner would not have rejected the claims even under the lower preponderance of evidence standard.

adapalene." (D.I. 331 at 38) Tolmar further contends "the inventors knew that their claims of unexpected results were false," because the inventors were aware that "other Galderma scientists previously concluded adapalene 0.3% was likely to be well tolerated and only slightly more irritating than adapalene 0.1%." (*Id.*) Hence, Tolmar asserts, the inventors "knowingly withheld from the Patent Office prior art information submitted to the FDA disclosing that 0.3% adapalene was found to be well tolerated based on these and later clinical trials." (*Id.* at 39)

Initially, the Court notes that it is unclear which materiality standard Tolmar seeks to apply in connection with its IND inequitable conduct theory. Tolmar notes that under *Therasense*, withheld prior art or information must be "but-for" material, i.e., sufficient to invalidate a claimed invention under the preponderance of the evidence standard. (*Id.* at 38) At the same time, Tolmar also notes that but-for materiality is not necessarily required for affirmative misrepresentations or other egregious conduct. Tolmar's post-trial briefing appears to invoke arguments relevant to both materiality standards. (*See, e.g.*, *id.* at 38-39) (describing "material misrepresentations to the Patent Office concerning 'unexpected results" and "knowingly with[olding] from the Patent Office prior art information submitted to the FDA disclosing that 0.3% adapalene was found to be well tolerated")[20] In light of this ambiguity, the Court will assess Tolmar's IND inequitable conduct allegations under both materiality standards.

1. No But-for Materiality

Under *Therasense*, "[w]hen an applicant fails to disclose prior art to the PTO, that prior art is but-for material if the PTO would not have allowed a claim had it been aware of the undisclosed prior art. Hence, in assessing the materiality of a withheld reference, the court must determine whether the PTO would have allowed the claim if it had been aware of the undisclosed

[20] Tolmar's inequitable conduct allegations may fall within that category of cases in which "it is often difficult to draw a line between nondisclosure and affirmative misrepresentation," as noted by the dissent in *Therasense*. 649 F.3d at 1314 n.3.

reference." 649 F.3d at 1291. As explained above in connection with the Court's obviousness analysis, Galderma's IND is unavailable as prior art because it is properly considered the inventors' or Galderma's own work. *See* 35 U.S.C. § 103(c); *Life Technologies, Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000). Accordingly, the statements on which Tolmar bases its inequitable conduct allegations – which are the same IND statements Tolmar cited in connection with obviousness – cannot be but-for material for inequitable conduct purposes, since the Patent Office could not have rejected the claimed inventions as obvious in view of these legally irrelevant statements.[21]

2. No Affirmative Acts of Egregious Misconduct

The Court agrees with Tolmar that Galderma's IND statements are potentially relevant for purposes of assessing whether statements to the PTO constituted affirmative acts of egregious misconduct that qualify as *per se* material under *Therasense*. If the Court were to find, based on the record evidence, that Galderma's own internal documentation was irreconcilably inconsistent with statements made to the PTO in support of patentability, such a finding might support a conclusion that Galderma's statements to the PTO were an affirmative act of egregious misconduct that warranted a finding of *per se* materiality. Thus, the Court has considered the statements in Galderma's IND to determine whether Galderma's subsequent statements to the PTO regarding the unexpected tolerability of 0.3% adapalene were, in fact, an affirmative act of egregious misconduct.

[21] As noted above in connection with the Court's obviousness analysis, the substantial differences between the claimed inventions and the studies described in Galderma's IND would not have provided any basis for rejecting Galderma's patent application even if those statements and studies had been disclosed. Moreover, in the Court's view, the Examiner would have understood that Galderma's IND statements were merely stating the hypothesis to be tested during the regulatory approval process, rather than reflecting any understanding derived from the prior art then in existence.

The Court concludes that Galderma did not commit any affirmative acts of egregious misconduct when representing to the PTO that the favorable tolerability profile of 0.3% adapalene was unexpected. Even assuming, *arguendo*, that the IND statements were not based on the inventors' own work, the Court agrees with Galderma that the IND statements were merely a statement of the hypothesis to be tested during the regulatory approval process. There is nothing irreconcilably inconsistent between stating a hypothesis *ex ante* and being genuinely surprised *ex post* when the hypothesis is proven correct.

3. No Intent to Deceive

In any event, Tolmar's inequitable conduct allegations based on Galderma's IND statements are without merit because Tolmar has failed to prove that the statements regarding unexpected results were made with an intent to deceive the Patent Office. There are multiple reasonable alternative inferences that may be drawn in connection with Galderma's IND statements, none of which lead to the conclusion that the inventors acted with an intent to deceive. The inventors could have reasonably believed that the statements in the patents regarding the surprising tolerability of 0.3% adapalene were directed to a person of ordinary skill in the art, rather than what the inventors knew subjectively based on their own inventive experience. Similarly, the IND statements regarding the expected tolerability of 0.3% adapalene were stating the hypothesis to be tested; they do not indicate any irreconcilable inconsistency with statements subsequently made to the PTO that would support a conclusion of deceptive intent.[22]

[22] The parties also dispute the significance of Dr. Graeber's trial testimony regarding whether he expected that 0.3% adapalene would be well tolerated. (Tr. at 609-10) Having observed Dr. Graeber provide that testimony, and having reviewed it again in transcript form, the Court agrees with Galderma's characterization of it. (D.I. 330 at 30-31)

C. "Rapid Onset" Language

Tolmar's "rapid onset" inequitable conduct allegation lacks merit. Galderma's statement regarding the more rapid onset of 0.3% adapalene was neither false nor misleading. The data reported in Galderma's patents merely state that 0.3% adapalene showed a more rapid onset than 0.1% adapalene. The Court agrees with Galderma that the patents correctly state that such a difference is noted, but do not claim that the difference was statistically significant or meaningful. (FOF 240)

D. "Statistically the Same" Language

Tolmar's final inequitable conduct allegation is directed to statements in the patents to the effect that the tolerability profiles for 0.3% and 0.1% adapalene, based on Phase II clinical trial data reported in the patents, were "statistically the same." According to Tolmar, Dr. Graeber admitted at trial that there was no basis to make any statistical statements regarding the relative side effect profiles because a statistical comparison was not performed. (Tr. at 614-17) Moreover, Tolmar argues, Galderma failed to disclose but-for material clinical trial data from Galderma's subsequent Phase III trials, which purportedly contradicted the Phase II results by demonstrating that the side effect profiles for 0.3% and 0.1% adapalene are statistically significantly different. Because Tolmar's theory appears to assert both the withholding of information and the affirmative misrepresentation of information, the Court will analyze Tolmar's allegations under both standards for materiality.

1. No But-for Materiality

The alleged failure to disclose the Phase III clinical trial data was not but-for material. The Court is persuaded by Galderma's arguments and evidence that the Phase III data allegedly withheld by Galderma is not but-for material because it does not, ultimately, contradict or refute

the statements made in the patents regarding the tolerability profiles of 0.3% and 0.1% adapalene being "statistically the same." In reaching this conclusion, the Court accepts Galderma's explanation that the phrase "statistically the same," as used in the specification of the patents-in-suit, means "not statistically significantly different." The person of ordinary skill in the art is not a mathematician, and Galderma identified scientific publications one of ordinary skill in the pertinent art might consult which use the phrase "statistically the same" to signify no statistically significant difference. (FOF 246) The Court also agrees with Galderma that the Examiner allowed the patents based not on any statistical claims regarding the side effects of 0.3% versus 0.1% adapalene, but rather on the general observation that 0.3% adapalene was more effective than 0.1% adapalene while ***minimizing*** side effects, regardless of whether the side effects were statistically the same. (FOF 249) Finally, the Court is not persuaded that the Examiner would have rejected the asserted claims even if the Phase III data had been disclosed.

2. No Affirmative Egregious Act of Misconduct

For similar reasons, the Court concludes that the "statistically the same" language does not rise to the level of an affirmative egregious act of misconduct. To the contrary, the data reported in the patents-in-suit are consistent with the data reported in the U.S. Phase III and the European clinical trials. (FOF 27, 262)

3. No Intent to Deceive

Tolmar's "statistically the same" inequitable conduct fails for the additional reason that the evidence does not persuade the Court that the inventors acted with an intent to deceive the PTO. Deceptive intent is not the single most reasonable inference that can be drawn from the record evidence. To the contrary, there are multiple, alternative inferences that would reasonably explain the statement in the patents-in-suit. Neither the inventors, the prosecuting attorneys, nor

the Examiner were statisticians by training; any confusion over the distinction between "statistically the same" and "not statistically significantly different" may reasonably be attributed simply to a misunderstanding over the use of such terminology. Under these circumstances, particularly as the alleged deception rests on such a subtle distinction, the Court does not find it reasonable to infer an intent to deceive. Furthermore, Dr. Graeber's publication of the Phase II and U.S. Phase III data is inconsistent with a finding of intent to deceive. *See Cancer Research Tech. Ltd. v. Barr Labs., Inc.*, 625 F.3d 724, 734 (Fed. Cir. 2010) ("[T]he prompt publication of data in multiple articles over the entire course of prosecution is inconsistent with finding that intent to deceive is the single most reasonable inference . . . ."). (D.I. 330 at 38-39) Finally, the Court had ample opportunity to assess inventor Graeber's credibility and observed nothing that suggests that his testimony was in any respect untrue.

VI. INFRINGEMENT UNDER THE DOCTRINE OF EQUIVALENTS

Tolmar contends that its proposed ANDA product does not infringe Claim 27 of the '060 patent under the doctrine of equivalents. The parties' dispute turns on whether the poloxamer 182 in Tolmar's proposed product is equivalent to the poloxamer 124 recited in claim 27, and whether prosecution history estoppel bars Galderma from asserting infringement under the doctrine of equivalents.[23] The Court addresses each dispute below.

A. Poloxamer 124 and Poloxamer 182

Poloxamer 124 and 182 are equivalent in the context of the '060 patent because they perform substantially the same function, in substantially the same way, to achieve substantially

[23] Tolmar has stipulated to infringement of claims 35 and 36 of the '181 patent, claims 40 and 41 of the '044 patent, claim 5 of the '558 patent, and claim 24 of the '060 patent. Galderma has stipulated to no literal infringement of claim 27 of the '060 patent in view of Tolmar's use of poloxamer 182 instead of poloxamer 124 in its proposed product. Tolmar has conceded that it will induce infringement of claim 27 of the '060 patent if that claim is held valid and enforceable, poloxamer 182 is found equivalent to the poloxamer 124, and prosecution history estoppel does not apply.

the same result. Tolmar does not seriously dispute that both poloxamers are equivalent under the function and result prongs. Tolmar's focus is on whether both poloxamers function in substantially the same way.

The Court is persuaded that poloxamers 124 and 182 act as wetting/dispersion agents in substantially the same way, to ultimately achieve the same result. Galderma presented credible expert testimony from Dr. Walters to the effect that both poloxamers function as wetting/dispersing agents through the common mechanism of steric hindrance. (FOF 325) While Tolmar highlights certain differences between poloxamer 124 and 182, those differences are insubstantial as they are irrelevant to both poloxamers' function, way, and results in the context of Tolmar's proposed ANDA product. (FOF 324-25)

B. Prosecution History Estoppel Is Not Proven

Tolmar further argues that prosecution history estoppel bars Galderma from asserting that the two poloxamers are equivalent. The Court disagrees.

Initially, the Court is not persuaded that prosecution history estoppel would apply to the original amendment made during prosecution of the '377 application. The rationale for the amendment was only tangentially related to the equivalent in question, as is evident from the Examiner's statement that poloxamer 182 was also known in the art as poloxamer 124. (FOF 339) The Court agrees with Galderma that "[t]here is nothing in the prosecution history that indicates that the reason these [amended] claims were allowed was due to the recitation of poloxamer 124 or its specific amount as opposed to the entirety of the combination." (D.I. 316 at 47)

Even assuming, *arguendo*, that prosecution history estoppel arose in the context of the '377 patent, any such estoppel would not extend to Claim 27 of the '060 patent, which involves a

completely separate patent, with an original claim that was not amended during prosecution, and which contains different limitations than those recited in the '377 patent.

Accordingly, Tolmar's proposed ANDA product infringes Claim 27 of the '060 patent.[24]

VII. STANDING

Tolmar contends that only one of the named co-plaintiffs in this action, Galderma R&D, has standing. According to Tolmar, Galderma S.A. and Galderma Labs lack standing as co-plaintiffs because they are merely non-exclusive licensees. *See Sicom Sys., Ltd. v. Agilent Techs., Inc.*, 427 F.3d 971, 976 (Fed. Cir. 2005) (noting that status as "nonexclusive license confers no constitutional standing on . . . [such] licensee to bring suit or even to join a suit with the patentee"). Hence, Tolmar asks the Court to dismiss Galderma S.A. and Galderma Labs for lack of subject matter jurisdiction. *See* Fed. R. Civ. Proc. 12(b)(1).

The parties' dispute arises from three agreements among the three named co-plaintiffs. The first agreement, dated June 1, 1995 ("the 1995 agreement"), grants a non-exclusive license from CIRD Galderma – the predecessor of Galderma R&D – to Galderma S.A., to "use CIRD's patents and Know-how to make, have made, and sell the PRODUCTS listed in Schedule 'A' in the Territory." (FOF 299) Schedule A, in turn, specifies that the licensed product is Adapalene Gel, known under Galderma's trademark Differin.®[25] "Know-how" is defined to include "patents." (FOF 301)

The second agreement, dated January 1, 1998 ("the 1998 agreement"), purports to grant an exclusive license from Galderma S.A. to Galderma Labs, "to make, have made, and sell the Products under the Trademarks in the Territory during the period of this Agreement," and defines the Products as including Differin®. (FOF 305) The "Territory" includes the United

[24] In view of the Court's ruling, the Court also denies Tolmar's motion for judgment on partial findings under Rule 52(c). (D.I. 312)

[25] It appears undisputed that the "Territory" includes the United States.

States. (*Id.*) On June 19, 2007, the 1998 agreement was amended to include Differin® Gel, 0.3% ("2007 Amendment"). (FOF 308)

The third, and final, agreement, dated December 23, 2004 ("the 2004 agreement"), grants an exclusive license from Galderma R&D to Galderma S.A., for the "know-how, processes, methods, formulas, recipes, and manufacturing secrets, patented or not, current or future, relating to the manufacture of the active ingredient Adapalene," and for the sale of the active substance Adapalene in the U.S. market. (FOF 302-04)

Tolmar offers several arguments for its position that Galderma S.A. and Galderma Labs are mere non-exclusive licensees who lack standing to enforce the patents-in-suit. First, Tolmar contends that the 1995 agreement only covers Differin® 0.1% Gel because, at the time the agreement was executed, only 0.1% adapalene gel was sold under the trade name Differin®, and the 1995 agreement was never amended to cover 0.3% adapalene gel. Second, Tolmar argues that even if the 1995 agreement were construed to include 0.3% adapalene gel, Galderma S.A. could not have granted an exclusive sub-license to Galderma Labs for rights to 0.3% adapalene because – at the time Galderma S.A. and Galderma Labs executed their 1998 agreement – Galderma S.A. itself possessed only non-exclusive rights to adapalene under the 1995 agreement. Third, and finally, Tolmar contends that the scope of the exclusive license set forth in the 2004 agreement is limited to "active ingredient Adapalene" and, therefore, does not include the claimed inventions at issue in this litigation, which relate to pharmaceutical compositions and methods, rather than just the active ingredient adapalene.

Having reviewed the parties' arguments and evidence, the Court concludes that Galderma S.A. has standing as an exclusive licensee to Differin® Gel, 0.3%, but Galderma Labs lacks standing because it is a non-exclusive licensee.

A. Galderma S.A. Has Standing

The parties do not dispute that the 2004 agreement confers an exclusive license to 0.3% adapalene concentrations; their dispute concerns whether the 2004 agreement is limited to the active ingredient adapalene or whether the scope of the exclusive license also includes the 0.3% adapalene products at issue in the present litigation.

The relevant provisions of the 2004 agreement support Plaintiffs' position. Article 1 of the 2004 agreement provides as follows:

> Galderma R&D grants to Galderma SA an exclusive license for North America (United States) to the set of know-how, processes, methods, formulas, recipes, and manufacturing secrets, patented or not, current or future, relating to the manufacture of the active ingredient Adapalene . . . .
>
> Galderma R&D likewise grants to Galderma SA an exclusive right to sell the active substance Adapalene for the North American market.

(FOF 304)

This language broadly includes adapalene products and is not narrowly limited to the active ingredient adapalene. Article 1 uses inclusive language, defining the scope of the exclusive license as extending to subject matter "relating to" – not "limited to" – the manufacture of the active ingredient adapalene. In the Court's view, 0.3% adapalene gel products, such as Differin® Gel, 0.3%, "relate to" the manufacture of the active ingredient adapalene, and, thus, fall within the scope of the 2004 exclusive licensing agreement between Galderma R&D and Galderma S.A. It follows that Galderma S.A. has standing as an exclusive licensee to the claimed inventions of the patents-in-suit.

B. Galderma Labs Lacks Standing

Tolmar contends that, even though the 1998 agreement purports to grant an exclusive sub-license from Galderma S.A. to Galderma Labs relating to 0.3% adapalene,[26] the 1998 agreement did not accomplish this objective because, at the time it was executed, Galderma S.A. itself possessed only non-exclusive rights to adapalene. Therefore, at the time, Galderma S.A. could transfer only non-exclusive rights.

Plaintiffs respond that the 2004 agreement between Galderma R&D and Galderma S.A. amended the 1995 agreement between Galderma R&D and Galderma S.A. To Plaintiffs, the 2004 agreement retroactively conferred exclusive rights in 0.3% adapalene to Galderma S.A., such that the 1998 sub-license from Galderma S.A. to Galderma Labs effectively rendered Galderma Labs an exclusive licensee.

The Court agrees with Tolmar that Galderma has failed to meet its burden of establishing that Galderma Labs is an exclusive licensee. *See Tyco Healthcare Group LP v. Ethicon Endo-Surgery, Inc.*, 587 F.3d 1375, 1378 (Fed. Cir. 2009) ("A plaintiff generally has the burden of proving standing to sue."). Although the 2004 agreement references the earlier 1995 agreement, the 2004 agreement neither states nor suggests that Galderma R&D and Galderma S.A. intended the 2004 agreement to serve as a retroactive modification or amendment to their earlier 1995 agreement. Rather, the 2004 agreement reads as if it is an entirely separate agreement. Moreover, even if Galderma R&D and Galderma S.A. had intended the 2004 agreement to serve as a retroactive modification or amendment of their ***1995*** agreement, there is no indication in any of the three relevant licensing agreements that any of the parties also intended for the 2004

[26] The parties do not appear to dispute that the 1998 agreement was amended in 2007 to cover Differin® Gel 0.3%. (*See* PTX 55)

agreement to retroactively modify the ***1998*** agreement between Galderma S.A. and Galderma Labs (the agreement on which Galderma Labs relies for its rights to 0.3% adapalene).

Therefore, because Galderma Labs never obtained exclusive licensing rights to adapalene, it lacks standing as a co-plaintiff for purposes of the present litigation. The Court will dismiss Galderma Labs as a plaintiff for lack of subject matter jurisdiction.

VIII. EXCEPTIONAL CASE

Finally, the Court rejects Tolmar's contention that this is an "exceptional case" within the meaning of 35 U.S.C. § 285 warranting an award to Tolmar of its reasonable attorneys' fees. As an initial matter, Tolmar is not the "prevailing party," other than with respect to a portion of its standing defense. Second, the Court does not find that Galderma's obtaining a 30-month stay based on the '377 patent and subsequent non-assertion of the '377 patent at trial to be the type of "exceptional" litigation conduct that justifies an award of attorneys' fees. To the contrary, Galderma's evolving strategy with respect to the '377 patent was predicated upon its reasonable claim construction positions, on which the Court did not rule until shortly before trial. Third, there is nothing in the record to support any conclusion other than that Galderma acted throughout in good faith. Tolmar's reliance on "the record of inequitable conduct committed by the inventors" as "justif[ying] treating this case as exceptional" (D.I. 317 at 50) is unfounded, as the Court has found no such inequitable conduct.[27]

CONCLUSION

The parties will be directed to submit a proposed order by which the Court may enter final judgment consistent with this Opinion.

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[27] To the extent Galderma, in its post-trial reply brief (D.I. 330 at 28, 49), seeks an award of its attorneys' fees pursuant to § 285, the Court rejects this request as well. The Court has not concluded that Tolmar's litigation tactics with respect to its evolving inequitable conduct allegations render this case exceptional.